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COMBINED MEDICAL AND SURGICAL MANAGEMENT OF UPPER GASTROINTESTINAL HEMORRHAGE*

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MANY excellent reviews of the problems in management of upper gastrointestinal bleeding have been presented by various internists and surgeons. Almost without exception the material has been analyzed from the point of view of the internist or the surgeon. Rarely has the combined approach been presented, although recent papers by Jones,[1] Heuer,[2] Schatzki[3] and Hoerr[4] have emphasized this. It is our purpose to demonstrate that the most efficient way to deal with massive bleeding is by means of a combined medical and surgical team in conjunction with a well trained roentgenologist. In the Veterans Administration Hospital, West Roxbury, such a team has been in existence during the past two and a half years.

MATERIAL

Although a combined medical and surgical responsibility in the therapy of upper gastrointestinal bleeding is most applicable when the source of hemorrhage is a peptic ulcer, the matter of diagnosis is so implicated with that of treatment that such a team must inevitably consider in some degree all causes of the hemorrhage. During the period from July 1, 1946, to June 30, 1948, 10,342 patients were admitted to the hospital, of whom 181 had upper gastrointestinal bleeding as their primary complaint. It has been convenient to divide these patients into three groups — massive, intermediate and slight — according to the severity of the hemorrhage. The massive group was composed of 86 patients and included those in whom the red-cell count fell below 3,000,000. The intermediate group, in which hemorrhage was sufficient to effect a fall in the red-cell count to less than 4,000,000 but greater than 3,000,000, contained 50 patients. In addition, 45 cases of slight hemorrhage occurred in which the red-cell count did not fall below 4,000,000. Of total hospital admissions 1.7 per cent were for upper gastrointestinal bleeding, 0.8 per cent being for massive hemorrhage. During the same period 494 patients with simple or complicated peptic ulcer were admitted to the hospital, 117, or 23 per cent, for hemorrhage. Of the 86 cases of massive hemorrhage 56, or 65 per cent, were demonstrated to be due to peptic ulceration, whereas the remaining 30 were due to esophageal varices, gastritis or undetermined conditions. Table 1 illustrates the dispersion of the cases according to source of the hemorrhage; the various diagnoses listed in the cases without ulcer are similar to those observed in other clinics (Hoerr[4] and Stolte[5]). It is of interest that in 15 per cent of the patients no site of origin of the hemorrhage could be demonstrated, and that in only 3 of these 14 patients could a history suggestive of ulcer be obtained. Reports from other clinics also contain a seemingly irreducible number of patients who must be put in this undiagnosed group. The origin of their hemorrhages will probably always remain obscure.

In 65 per cent of patients admitted for massive upper gastrointestinal bleeding the source was demonstrated to be a peptic ulceration. Among this group 85.7 per cent of cases were due to duodenal ulcer, 12.6 per cent to gastric ulcer, and 1.7 per cent to marginal ulcer. The ratio of these three types of ulcers to each other is comparable with that found in any group of ulcers whether bleeding or not. In the intermediate and slight groups a similar ratio of bleeding due to ulcer and other conditions was obtained.

MORTALITY

Eleven of our 86 patients with massive upper gastrointestinal hemorrhage died — a mortality of 12.8 per cent. Only 2 of these were in the ulcer group of 56 patients (a mortality of 3.6 per cent for massively bleeding peptic ulcer). Nine of 30 patients with massive bleeding from conditions

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other than ulcer died, however — a mortality of 30 per cent. Table 2 reveals the causes of death in the 11 cases of massive bleeding. Two facts of interest stand out here. The first is that in only 6 of the 11 cases was hemorrhage the primary cause of death. In the other 5 the patients died of other causes — liver failure in 3, peritonitis and malnutrition in 1, and terminal carcinoma of the stomach in 1. Secondly, 10 of the 11 patients who died had either hepatic cirrhosis or portal hypertension as a primary or secondary diagnosis. In the 3 of these 10 that were not bleeding frankly from esophageal varices the sources of bleeding were gastric ulcers in 2 and undetermined in 1. From these facts it appears that one must agree with the conclusion of Meulengracht[6] that the dangerous bleeders are those whose bleeding is due to or complicated by factors that interfere with nutrition or the normal state of the gastrointestinal blood vessels. Arteriosclerosis is undoubtedly the most common unfavorable complicating factor that renders the hemorrhage dangerous. We believe, however, that it is not the only one. Others, such as portal hypertension and hepatic cirrhosis, were important in our series. One of the 2 deaths from massive bleeding in peptic ulcer occurred in a twenty-six-year-old man with a gastric ulcer who died, two days after an emergency operation, of lobar pneumonia. Here arteriosclero played no part, but portal hypertension, whi had developed after a traumatic portal-vein throm bosis, and pneumonia made the bleeding ultimate fatal. The second death from ulcer was in a sixty seven-year-old man with a gastric ulcer, advance

TABLE 1. *Upper Gastrointestinal Bleeding in Patients with and without Ulcer.*

DIAGNOSIS	MASSIVE HEMORRHAGE		INTERMEDIATE HEMORRHAGE		SLIGHT HEMORRHAGE		TOTAL CASES	TOTAL DEATHS
	NO. OF CASES	NO. OF DEATHS	NO. OF CASES	NO. OF DEATHS	NO. OF CASES	NO. OF DEATHS		
Patients with peptic ulcer:								
Duodenal ulcer	48	0	29	1*	26	0	103	1
Gastric ulcer	7	2	3	0	0	0	10	2
Marginal ulcer	1	0	1	0	2	0	4	0
Totals	56	2	33	1	28	0	117	3
Patients without ulcer:								
Esophageal varices	8	7	3	0	2	0	13	7
Gastritis	6	0	6	0	7	0	19	0
Other†	2	2	1	1	0	0	3	3
Cause undetermined	14	0	7	0	8	0	29	0
Totals	30	9	17	1	17	0	64	10
Grand totals	86	11	50	2	45	0	181	13

*The primary cause of death was hypertensive cardiovascular disease.

†These diagnoses were carcinoma of the stomach; cirrhosis without demonstrable varices; and leiomyoma of the stomach.

cirrhosis and carcinoma of the liver, death occurring within thirty-six hours of admission to the hospital.

MANAGEMENT

All patients with gastrointestinal hemorrhage were admitted to the Medical Service, but within twenty-four hours of arrival and as soon as the diagnosis of massive hemorrhage had been made the patient was seen by the surgical member of the team, who then followed the case with frequent consultations with the internist.

Diagnosis

Since the accurate diagnosis of the source of the bleeding was an important determination if any surgical therapy was to be undertaken, special attention was paid to the diagnosis as obtained by the usual methods and to the reliability thereof. In addition, a study was made in the cases of massive hemorrhage of certain special considerations such as previous diagnoses, habits, type of bleeding

TABLE 2. *Causes of Death in Patients with Upper Gastrointestinal Hemorrhage.*

PATIENT	AGE	SOURCE OF HEMORRHAGE	AUTOPSY	DEGREE OF HEMORRHAGE	CHIEF CAUSE OF DEATH	OTHER DIAGNOSES
	yr.					
H. W. L.	26	Gastric ulcer	Yes	Massive	Hemorrhage	Portal hypertension; pneumonia.
E. P. M.	67	Gastric ulcer	Yes	Massive	Hemorrhage	Cirrhosis of liver; liver-cell carcinoma.
W. G. M.	55	Esophageal varices	Yes	Massive	Cirrhosis of liver	Hemorrhage
T. P. J.	52	Esophageal varices	Yes	Massive	Cirrhosis of liver	Hemorrhage; arteriosclerotic heart disease.
A. P.	35	Esophageal varices	Yes	Massive	Hemorrhage	Cirrhosis of liver; rectal varices, with rupture.
F. W. P.	59	Esophageal varices	Yes	Massive	Peritonitis	Portal-vein thrombosis; hemorrhage.
P. M.	54	Esophageal varices	Yes	Massive	Hemorrhage	Cirrhosis of liver
T. H.	52	Esophageal varices	No	Massive	Hemorrhage	Cirrhosis of liver
J. R. G.	43	Esophageal varices	Yes	Massive	Hemorrhage	Cirrhosis of liver
J. J. G.	57	Carcinoma of stomach	Yes	Massive	Carcinoma of stomach	Hemorrhage
W. A. B.	51	Gastric mucosa	Yes	Massive	Cirrhosis of liver	Hemorrhage

and response to conservative therapy that might prove of assistance in arriving at a correct diagnosis. The average ages in the ulcer and nonulcer group did not differ significantly, being forty-one and forty-four years respectively. Although the duration of bleeding prior to admission tended to be shorter and other evidences of severity of hemorrhage (fainting, sudden onset, hematemesis) tended to be more pronounced in the patients bleeding from esophageal varices than in the other groups, little statistical difference could be found between the ulcer and nonulcer groups if they were taken as a whole. Hematemesis was absent in a considerable number of each group but not enough in any one to help in distinguishing the various diagnoses in question. It was present in all the patients who died or were operated on and in 65 per cent of the patients with duodenal ulcer and massive hemorrhage. It occurred in only 40 per cent of the less severely bleeding ("intermediate") group. We must agree with Meulengracht[6] that in general the absence of hematemesis means, even if the ulcer is beyond the pylorus, a less serious degree of bleeding than if it is present.

Although in the ulcer groups some factors that caused emotional or physical strain or overtaxed the gastrointestinal tract were present in over half the patients before they bled from ulcer, the same conditions were observed in almost half the patients bleeding from other causes. The most common of these factors was overindulgence in food or alcoholic beverages or the assumption of unusual responsibility such as is attendant on a business reverse or crisis, an impending marriage or the moving of a household. Infections and the use of salicylates occurred as possible precipitants in both groups. In 60 per cent of the patients with ulcer there was a premonitory symptom of ulcer activity—that is, pain or vomiting. In the nonulcer group false signs of ulcer activity were present in only 4 cases, 2 of which were in the group in which no cause could be found; clinically, these patients were ulcer suspects even though x-ray films failed to show an ulcer crater. This finding is of importance in differential diagnosis and also has obvious prophylactic implications in that it behooves patients with ulcer to heed such symptoms early and to seek treatment promptly.

Sixty-eight per cent of all patients with ulcer who bled suffered ulcer pain during hemorrhage. Among the patients without ulcers there were 3 who had false ulcer pain. Two of these were ulcer suspects but had normal gastrointestinal x-ray films. The other patient also had bleeding of undetermined cause. This symptom, therefore, if present, is a helpful one in making the differential diagnosis between hemorrhage from peptic ulcer and that from other causes. Forty-seven of the 56 patients (84 per cent) with bleeding from peptic ulcer gave a history of previous symptoms of postprandial distress that could be interpreted as being due to ulcer. False symptoms, sufficient to have suggested a clinical diagnosis of ulcer, were present, however, in 11 of the 30 nonulcer bleeders (36.6 per cent), 10 of whom had gastritis or hemorrhage of undetermined cause. This degree of incidence among the nonulcer group suggests that a history of previous symptoms is unreliable in aiding differential diagnosis.

Among the patients with ulcer 35 had had a definite, previous diagnosis of ulcer, confirmed by x-ray study; among the patients without ulcers there were but 2 in whom the diagnosis had been made. A definite previous diagnosis of ulcer, if present, is therefore significant.

The incidence of previous hemorrhage in the patients studied was not significant. No conclusions can be drawn since slightly more than two thirds of our patients were admitted during their first hemorrhage and slightly less than a third during subsequent hemorrhages. Since gastritis is a condition generally associated with multiple hemorrhages, we were surprised to find that only 1 of these patients had bled previously before admission to the hospital.

The drinking habits of the 65 patients of the total of 86 in the series in whom an adequate history in this regard was obtainable are interesting. It is striking that 34, or more than half, of the patients were heavy drinkers, and that this applied to 17 of 21, or 81 per cent, of the nonulcer group, and to 17 of 44, or 38.6 per cent, of the ulcer bleeders. It is of interest that only 1 patient of 21 in the nonulcer group was an abstainer. None of these distinctions, however, were clear-cut enough to help us definitely with differential diagnosis in the individual case.

Physical Examination

The physical examination included inspection for the so-called ulcer facies, a careful search for stigmas of cirrhosis—namely, a large, percussible or palpable liver or spleen and jaundice— and inspection of the face, shoulders, arms and back for spider telangiectasias. It was discovered that during the height of hemorrhage and shock, enlarged spleens were often too soft to be felt, and spider telangiectasias too faint to be visible. The degree of arteriosclerosis was always estimated.

Hemoglobin, red-cell counts and hematocrit determinations were made daily as long as signs of hemorrhage persisted and at less frequent intervals thereafter. As soon as possible, determinations were made to rule out the presence of a hepatic or metabolic disturbance.

Emergency X-ray Study

The early roentgenologic examination in patients bleeding from the gastrointestinal tract was initiated by Hampton[7] and has been discussed by Schatzki,[3] who gives a thorough description of the technic. Here we shall only mention in brief that a thin

barium suspension was used, that the patient was examined in the prone and supine positions only, and that compression technic was not employed. Our indications for such emergency x-ray examination were as follows: persistent or recurrent bleeding in a patient on whom we were prepared to perform urgent surgery if the diagnosis of ulcer was definitely established; recurrent bleeding in a patient in whom previous studies had failed to determine the source of the hemorrhage. In each case the surgical member of the team agreed to the need of emergency x-ray examination, an adequate stock of matched blood for transfusions was on hand, but six hours later on the ward, and was not fatal. Another patient, a man of fifty-six, entered the hospital with a massive hemorrhage and gave a history of having had a duodenal ulcer for years. To corroborate this he gave a history of having had a perforation sutured six months before and demonstrated an abdominal scar to prove it. Since he was in the older age group and did not respond to medical therapy within forty-eight hours, operation was strongly considered and planned. An emergency barium meal was thought by many to be superfluous in this case. It was performed, however, and large esophageal varices were seen,

TABLE 3. *Results of Operation.*

PATIENT	AGE	DIAGNOSIS	TYPE OF OPERATION	RESULT
	yr.			
Emergency procedure:				
H. W. L.	26	Gastric ulcer; portal hypertension	One-stage gastrectomy	Death 2 days after operation from lobar pneumonia
Urgent procedures:				
C. A.	55	Duodenal ulcer; malnutrition; early cirrhosis.	One-stage gastrectomy, without excision of ulcer	Excellent
J. J. C.	60	Duodenal ulcer	One-stage gastrectomy	Excellent
F. W. C.	39	Duodenal ulcer	One-stage gastrectomy	Excellent
T. R. C.	40	Duodenal ulcer; extensive penetration with inflammatory mass.	Two-stage gastrectomy	Excellent
T. H. F.	49	Duodenal ulcer; extensive penetration with inflammatory mass.	Two-stage gastrectomy	Excellent
J. W. F.	60	Duodenal ulcer; cholelithiasis and cholecystitis.	One-stage gastrectomy	Excellent
E. J. L.	57	Duodenal ulcer; extensive penetration following recent perforation.	One-stage gastrectomy	Excellent
C. O.	56	Duodenal ulcer; diabetes mellitus.	One-stage gastrectomy	Excellent
J. P. M.	53	Gastric ulcer; extensive pancreatic penetration.	One-stage gastrectomy, without excision of ulcer	Excellent
J. L. S.*	52	Undetermined cause	Exploration; no source of bleeding found.	Excellent

*This case is discussed in detail in the text.

and a room was available in the operating suite for the immediate transfer of the patient should further hemorrhage occur or a lesion be found that would indicate that early operation was necessary. All emergency x-ray examinations were rechecked six to twelve days after bleeding had ceased. Of our 86 patients 19, or 22 per cent, had an emergency gastrointestinal series performed during bleeding. In 17 of these patients a satisfactory examination was obtained and a diagnosis made either by positive findings or by exclusion, no additional information being obtained by subsequent elective x-ray study. In 1 patient the examination was unsatisfactory and was recognized as such, so that therapy was not thereby influenced. In another, the first case of the series (J. L. S., Table 3), a possible diagnosis of duodenal ulcer was made. This was not found at an urgent operation performed on the basis of these x-ray findings. Review of the films taught us that a minimal degree of deformity of the duodenum seen in a gastrointestinal series performed under emergency circumstances cannot be taken as positive evidence of ulcer. In 1 patient only the examination may have contributed to a recurrence of bleeding. This took place not in the X-Ray Department only a slight deformity being present in the duodenum. Conservative therapy was persisted in and was successful in stopping the hemorrhage; the diagnosis was then further substantiated during a subsequent successful splenorenal anastomosis. In retrospect, if the very positive history of ulcer had been acted upon the patient would have received an unnecessary emergency operation.

Gastroscopy

Gastroscopy was performed as an urgent procedure only during second or repeated admissions of the patients in whom no source for the bleeding had been found by elective examinations during the previous periods of hospitalization. It was helpful in 2 cases, and perhaps should have been utilized more frequently.

TREATMENT

Conservative treatment as initiated on the medical ward did not differ in great extent from that in current practice in the United States. The pulse, blood pressure and blood counts were taken at frequent intervals depending upon the briskness of hemorrhage and the degree of shock. A chart of all stools and vomitus was made. If a history

of hematemesis or other vomiting within twelve hours of admission was obtained the patient was starved rather than fed. Similarly, patients with esophageal varices were not fed until the immediate bleeding and shock had been controlled. Feedings, when initiated, were of small amounts and of the softest types of foods. Careful sedation was carried out by the combined use of small doses of sodium luminal and various narcotics. Early in the series morphine was used rather extensively, but owing to the frequent vomiting that resulted from the use of more than 10 mg. (1/6 gr.) of this drug a shift to Demerol in 50-mg. doses subcutaneously was made and found to be most satisfactory. The early recognition of the cirrhotic patient is most important, since minimal sedation is necessary in this group to avoid the precipitation of hepatic coma. Transfusions were the backbone of the replacement therapy and were given liberally not only to prevent shock but also to restore promptly a sufficient volume of blood so that the red-cell count would be elevated above 3,500,000. The parenteral injections of large doses of vitamins C and K were arbitrarily employed in patients with chronic peptic ulcer who had been on rigid feeding regimes for a long time. Fifty-three and 56 per cent, respectively, of the patients with and without ulcer stopped bleeding within twenty-four hours of admission. Forty per cent of the latter continued to bleed, compared to 21 per cent of the former. In 23 per cent of the patients with ulcer bleeding recurred after having once stopped, and only 1 nonulcer patient experienced a recurrence in bleeding. This is in keeping with our conception of bleeding from peptic ulcer — namely, that the reason for continuation of bleeding is the redigestion of the clot from the bleeding vessel by the strong acid and peptic secretion of the gastric mucosa in the patient with ulcer. A patient who stops bleeding early under medical treatment and then bleeds again may, from this data, be considered more likely to have a peptic ulcer than some other condition as a cause of his bleeding.

Surgical

Surgical operation was carried out in 10, or 18 per cent, of the patients with proved peptic ulcers. From a previous study of the literature (Warren and Lanman[8]) it was apparent that under the best conservative methods available there has always been an irreducible minimum of 1 or 2 patients out of every 20 with massive bleeding from ulcer who do not survive conservative therapy. These patients usually either are elderly or have some specific complicating factor besides the ulcer itself. We have considered it impossible to determine which of the patients in these groups is going to stop bleeding on medical therapy without spending many days in a therapeutic trial, which, if unsuccessful, leaves the patient in a poor state for operation. We have adopted, as the result of our experience, a policy of operating at an early period on all patients over approximately forty years of age with bleeding from peptic ulcer that does not stop within forty-eight hours of entry or, having once stopped, begins again to an appreciable degree. In addition, operation was seriously considered on the basis of the same temporal indications when the diagnosis of extensive penetration was made or a complicating disease such as cirrhosis or diabetes mellitus was present. Wood[9] has recently pointed out the high incidence of bleeding in diabetic patients with ulcer. This policy necessitates the inclusion in the operative group of many patients who would have stopped bleeding on a medical regime had it been continued. It is only justifiable, then, if it includes all the patients whose hemorrhage would not have stopped on a medical regime. This we believe to be the case with the exception of the rare patient who exsanguinates within forty-eight hours of admission.

We have believed that, to justify a policy of urgent operation on a selected group of patients, rigid requirements must be insisted upon. The diagnosis must have been confirmed by x-ray study and, to decrease the risk, the operation performed must be simplified in certain patients. For example, in comparison with the conventional gastric resection it may occasionally be considered wiser, in patients in whom the ulcer is very difficult to remove because it lies posteriorly in the gastroduodenal segment, to leave that ulcer in situ (Warren and Lanman[8]). In the latter instance, although it has not occurred in our experience, recurrent hemorrhage from the ulcer that has not been removed has been described (Welch[10]). We consider, however, that having performed such a procedure in a patient bleeding from duodenal ulcer and the ulcer having bled again, one is in a stronger position than if such a (first-stage) procedure had not been done. In the first place we have assurance that the ulcer will heal within a few weeks at the longest (McKittrick, Moore and Warren[11]) and, secondly, if, rarely, further surgery seems advisable to stop hemorrhage, it can be done with the attention focused thoroughly on this objective. It helps the surgeon greatly to know that no gastrojejunal anastomosis need be done after eradication of the ulcer has been performed, and also that the patient can eat enough to maintain nutrition soon after operation. This is essential if liver disease is present.

The group of patients, all "proved" cases of ulcer, in whom the decision to operate was made, are shown in Table 3. The operations were graded as emergency when the patient's hemorrhage continued faster than replacement therapy could restore it, and urgent when bleeding was continuing but at a slow enough rate so that a red-cell count of 3,500,000 or higher could be restored before operation was begun. The 1 death, in a case of gastric ulcer

with severe portal hypertension, was the emergency case and has been discussed above. Of the 10 patients whose operations were regarded as urgent 4 had extensive penetrations with large inflammatory masses; 2 were complicated by liver or biliary-tract disease, and 1 was a diabetic patient. Two others were aged thirty-nine and sixty years, but had no specific complications of their duodenal ulcers. The tenth patient (J. L. S., Table 3) has been referred to above. It is impossible to estimate how many of these patients would have survived if conservative treatment had been continued, but from our previous clinical experience we believe that not over half the group would have survived.

Discussion

From these studies our ability to make a differential diagnosis of upper-gastrointestinal-tract hemorrhage at the time of active bleeding on clinical grounds alone is limited. It can be made fairly accurately if one weighs carefully certain positive and negative findings of the history and physical examination. Two unusually helpful and accurate facts in the diagnosis of peptic ulcer in our series were a previous diagnosis of ulcer by a physician and the presence of pain during the bleeding episode.

Our attitude toward emergency x-ray examination is that it is the one indispensable maneuver in the diagnosis of the source of bleeding, but that although it is generally a safe procedure it is not necessary unless the x-ray findings are to change any course of therapy that has already been instituted. This obviously applies to its place in the selection of patients in whom surgical rather than medical therapy will be undertaken.

The majority of patients with hemorrhage of various degrees of severity continue to be successfully treated by conservative methods, the backbone of which is adequate blood replacement. Almost invariably the cases of ulcer in which the patients do poorly are those complicated by some additional disease. This may be vascular, hepatic or metabolic, but its prompt recognition by the internist is essential if he and the surgeon are to make an intelligent decision regarding the method of therapy. Thus, an earlier and more radical surgical approach to the bleeding ulcer complicated by arteriosclerosis, cirrhosis or portal hypertension, diabetes or penetration resulted in a lower mortality than we believe would have occurred had such a policy not been in effect.

Summary

A combined medical and surgical team directed therapy in 86 cases of massive upper gastrointestinal hemorrhage, 56 of which were due to peptic ulceration. The mortality of the patients with ulcer was 3.6 per cent, and that of the nonulcer bleeders 30 per cent.

Emergency gastrointestinal x-ray films were taken when the course of the bleeding or the presence of certain complications suggested that urgent operation might be performed if the presence of an ulcer as the source of the hemorrhage could be definitely established. Satisfactory x-ray films were obtained in 17 actively bleeding patients, and in only 1 case was the bleeding possibly aggravated by the procedure.

Urgent operation was successfully carried out in 9 cases after the establishment of a definite diagnosis of peptic ulcer. An additional patient was operated on as an emergency, and died two days postoperatively. These patients had been selected because of continued bleeding over forty-eight hours, age or the presence of certain complicating diseases, notably portal hypertension.

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BRILL'S DISEASE*

Report of 3 Cases with Aureomycin Treatment in 2

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PHILADELPHIA

BRILL'S disease should be considered as a cause of fever of undetermined origin in a general hospital that draws patients from the foreign-born population.

Typhus fever, a scourge of all times and all nations, was first differentiated from measles in Italy by Jerome Cardan in 1536. Bravo, in 1570, and Fracastorius, in 1584, further described the disease, though the cause was not surmised. In 1608 Cober described the "Hungarian disease," which was prevalent in that army, and noted the presence of lice infestation among soldiers but did not relate them etiologically to what apparently was epidemic typhus. Five hundred and three years later, Nicolle discovered that the body louse could transmit this disease from monkey to monkey. He also observed that in a hospital where the patients' clothing was removed on admission no cases of typhus developed, except among the attendants who handled the discarded infested clothing.

Epidemic typhus accompanies war, and during World War I it was prevalent in Serbia, Germany, Austria, Russia and Poland. This type of typhus is caused by *Rickettsia prowazeki*, which utilizes the body louse as the vector. A second variety of the disease, known as endemic typhus, is constantly prevalent in the southeastern United States. This malady is somewhat milder than the former and differs in that the vector is the rat flea.

A mild sporadic variety of typhus was reported in 1898 by Brill[1] in New York. By 1910 this investigator had collected and reported 221 cases.[2, 3] Zinsser,[4] in 1934, reviewed the subject and suggested that patients who had once lived in an area where an epidemic of typhus fever had occurred and in whom clinical symptoms resembling typhus later developed were manifesting an exacerbation of a long-dormant typhus infection.

Three cases, all in Russian-born persons admitted to the hospital with fever of undetermined origin, in which subsequent study established the diagnosis of Brill's disease are reported below. The patient in Case 1 was treated conservatively, whereas the latter 2 received aureomycin. The specific organism (*R. prowazeki*) was isolated in Cases 2 and 3.

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CASE REPORTS

CASE 1. S. P., a 40-year-old housewife, was admitted to the hospital on June 21, 1948, with a chief complaint of fever and headache and discharged on July 13.

The present illness had begun 11 days prior to admission with vague prodromes of fatigability and irritability. The onset of fever occurred 4 days prior to admission. While the patient remained at home, the temperature varied from 101 to 104°F., and this was accompanied by headache and sweating. Her physician treated her with sulfonamides and penicillin without effect, and she was admitted to the ward service.

The past history revealed that in 1921, at the age of 13, the patient had migrated to America from Kiev, Russia. As far as she could recall she had had no serious febrile diseases either in Europe or in this country.

Physical examination showed a well developed and well nourished but dehydrated woman, who did not seem dangerously ill. The pupils reacted to light and accommodation. Slight conjunctival injection was present. The chest was normal except for bronchial breathing over the right lower lobe. There was no lymphadenopathy. Rectal and pelvic examinations were negative.

The temperature was 104.4°F., the pulse 94, and the respirations 26 per minute. The blood pressure was 128/80.

During the first 36 hours the temperature ranged between 101 and 104°F., and nonspecific drugs with cooling sponges comprised the therapy adopted. On the 3rd morning the temperature dropped to 98.6°F., and a macular rash was noticed on both upper extremities and over the sides of the abdomen. This spread during the day to include the arms, forearms, upper part of the chest and back. The rash became maculopapular and discrete. The lesions were reddish, with some brownish discoloration. Twelve hours after it was first observed, the rash faded, leaving only slight pigmentation. The patient again became febrile, the temperature ranging between 102 and 103°F., and continued so until the 6th hospital day, when the temperature became normal and remained so until discharge.

On admission the patient was very irritable and complaining. On the morning of the 4th hospital day she became increasingly irritable, dull, drowsy and apathetic. She was unresponsive and appeared exhausted. After defervescence, she became clearer mentally and gradually regained her appetite, and it was possible to maintain hydration without intravenous administration of fluids.

Roentgenologic examination of the chest showed the lungs to be clear and well aerated. The right hilar markings were accentuated, but there was no evidence of pneumonitis. Electrocardiograms were normal.

Urinalysis and urine culture were normal on admission, but later, after pyuria developed, microscopical examination showed many pus cells and a hemolytic *Staphylococcus albus* and *Aerobacter aerogenes* grew on culture.

Examination of the blood showed a red-cell count of 4,480,000, with a hemoglobin of 14.8 gm., and a white-cell count of 10,350, with 76 per cent neutrophils, 1 per cent monocytes and 23 per cent lymphocytes. There were 71 per cent filamented and 29 per cent nonfilamented forms. During the course of the illness, the red-cell count dropped to 3,600,000, and the hemoglobin to 12 gm. The total white-cell and differential count remained stationary. The sedimentation rate was 54 mm. per hour (Wintrobe method). The blood Wassermann test was negative. The blood sugar, urea nitrogen and total protein were normal.

Blood cultures on admission and on three subsequent occasions failed to reveal any organism. A stool culture showed only colon bacilli.

The spinal fluid obtained at the height of the mental torpor was clear with a count of 9 lymphocytes per cubic millimeter. Culture failed to reveal any pathogens.

Attempts were made, beginning on the 9th day of fever, to isolate the causative rickettsia. Several samples of whole blood, the buffy coat of spun-down citrated blood and a bone-marrow specimen obtained from the sternal marrow were injected into animals. Three colonies of lice enclosed in special capsules were allowed to feed on the patient for varying periods, and animal inoculations were then done.

Isolation attempts by all these methods were unsuccessful. No rickettsia could be demonstrated.

Agglutination tests for *Eberthella typhosus* (strains O and H), paratyphoid A, paratyphoid B, brucellosis and *Proteus OX-19* were negative on admission and again 2 days later. On the 14th day of fever the agglutination for *P. OX-19* became positive in a titer of 1:320. On the 23rd day the titer increased to 1:640.

At the Virus Diagnostic Research Laboratory of the Children's Hospital of Philadelphia, complement-fixation tests were performed with the following results: the titers for epidemic typhus and murine typhus were, respectively, 1:64 and 1:16 on the 7th day and 1:2048 and 1:512 on the 15th day.

Confirmation was obtained by serologic studies made by the Army Epidemiological Board working at the Laboratories of Harvard School of Public Health under the direction of Dr. Edward S. Murray, who reported the results shown in Table 1. Thus there was serologic evidence of infection with the rickettsia of epidemic typhus.

She gradually regained her strength and well being and had no sequelae, with the exception of a mild pyuria beginning on the 15th day, undoubtedly subsequent to the repeated catheterizations.

She was seen for a follow-up examination 2 months after discharge and was clinically well.

Since the patient had had no recent exposure to the known vector of epidemic typhus this was assumed to be a case of Brill's disease.

TABLE 1. *Complement-Fixation Tests for Epidemic and Murine Typhus in Case 1.*

DAY OF TEST	EPIDEMIC-TYPHUS TITER	MURINE-TYPHUS TITER
7th	1:80	1:20
9th	1:640	1:80
14th	1:640	1:160
17th	1:1280	1:160
22nd	1:320	1:80
49th	1:320	1:80

CASE 2. A. F., a 41-year-old locksmith, was admitted to the Medical Service on January 22, 1949.

This patient had been well until 5 days before admission, when he complained of a toothache. On the following day he developed a headache, which persisted, together with malaise, nausea, vomiting and fever. Associated with these symptoms were abdominal distention and pain. On the next day, the temperature varied between 103 and 105°F. Three hundred thousand units of penicillin was administered daily for 4 days along with a sulfonamide. When seen at home by one of us just prior to admission, he presented a picture of febrile toxicity, the cheeks were flushed, the eyes dull, and the appearance then was strongly suggestive of typhoid fever. A fine reddish macular rash, which blanched on pressure, was observed on the trunk. Mouth hygiene was poor, and the gums bled easily on pressure. There was evidence of a pneumonitis at the right base. The abdomen was moderately distended, but no masses were felt.

Later that day, the patient was admitted to the hospital, and a more careful history and physical examination were possible. He complained of pains over the frontal area, beneath the sternum and generally over the abdomen. He was quite dehydrated, and the rash on the abdomen seemed more diffuse than it had been a few hours earlier. The edge of the liver was just palpable beneath the costal margin. A provisional diagnosis of septicemia arising from an infected tooth, virus pneumonitis or a rickettsial disease was made. It was further learned that the patient had been born in Kiev, Russia, and that at the age of 6 he had contracted either typhus or typhoid fever, probably the former. He had been entirely well until the present illness. He had come to the United States at the age of 16. His locksmith shop was located adjacent to a pet shop, where mice and rats were sold. With this history, the attention of the examining physician turned to the possibility that the patient was suffering with recrudescent epidemic typhus fever (Brill's disease).

On the next day, the toxicity persisted, the temperature remaining high (103°F.) and the pulse 100 per minute. On the 3rd day after admission, the rash seemed to fade on the abdomen but was still present on the arms and the legs. Lice colonies were implanted on the patient by Dr. Edward S. Murray, of the Army Epidemiological Board, working at the Laboratories of Harvard School of Public Health. Aureomycin was then begun on the 8th day of illness. One thousand milligrams was given for the first dose, followed by 750 mg. every 6th hour for 2 days, 500 mg. every 6th hour for 3 days and 250 mg. at like intervals for the next 2 days. In all, 13 gm. of aureomycin was administered over an 8-day period. The temperature fell to 100°F. 14 hours after the beginning of aureomycin therapy, but in the next 10 hours it rose to 104°F., remaining so for 8 hours, and then rapidly declined to normal on the 10th day of the disease. The patient continued to improve rapidly, was allowed out of bed on the 14th day and was discharged on February 6.

On the day after admission the red-cell count was 4,470,000, with 11.8 gm. of hemoglobin, and the white-cell count was 12,350, with 73 per cent neutrophils, 23 per cent lymphocytes and 4 per cent monocytes. A count of filamented and nonfilamented forms showed a marked shift to the left. The blood urea, chloride and sugar were within normal limits. Blood cultures repeated on three occasions were negative. Roentgenologic examination of the chest at the time of admission showed increased bronchovascular markings. A plain film of the abdomen was normal. An electrocardiogram showed a sinus tachycardia. Smears from the gums were positive for Vincent's organisms. A stool was negative for ova and parasites.

Capsules containing lice were implanted on this patient on the 7th day of illness for 13½ hours. Subsequently, these lice were placed on a normal rabbit for 11 days. At the end of this time, 120 lice remained alive. These were ground up and injected intraperitoneally into x-ray cotton rats. Five days later the rats were very sick, were killed and smears from their peritoneal exudate showed large numbers of intracellular and extracellular organisms, which when stained by the Macchiavello method were recognized as typical rickettsias. These rickettsias are now being further studied with immunity and other animal methods to differentiate them from murine-typhus strains. It seems from the clinical picture of this patient and from his history, that these rickettsias will be identified as the specific etiologic strain causing recrudescent epidemic typhus.

TABLE 2. *Complement-Fixation Tests in Case 2.*

DAY OF TEST	EPIDEMIC-TYPHUS TITER	MURINE-TYPHUS TITER
7th	1:512	1:128
10th	1:2048	1:1024
16th	1:2048	1:1024

On admission the agglutination tests for *E. typhosa* O and H, paratyphoid A, and paratyphoid B, *Brucella abortus* and *P. OX-19* were negative. On the 10th day of illness, the agglutination for *P. OX-19* was ++++ and +++, respectively, in dilutions of 1:20 and 1:40. On the 12th day of illness, the agglutinations for *P. OX-K* and *OX-2* were negative from a titer of 1:20 through 1:1280. On the 15th day of illness, tests for *P. OX-19* were positive in 1:320 dilution. On the 20th day of illness tests for *P. OX-19* were positive in dilutions of 1:20 to 1:80 but negative in dilutions of 1:160 to 1:320.

Serum was sent to the Virus Diagnostic Research Laboratory of the Children's Hospital, where complement-fixation tests were performed and the results shown in Table 2 were obtained.

This was the fifth case of suspected Brill's disease studied by the Army Epidemiological Board working at the Laboratories of Harvard School of Public Health in which rickettsial identification justified a positive diagnosis.

CASE 3. M. T., a 55-year-old contractor, was admitted to the hospital on April 21, 1949, with the chief complaint of chills and fever.

On March 27 the patient had been discharged from the Jewish Hospital after a colectomy and ileosigmoidostomy for carcinoma of the colon. Three weeks after discharge, during the convalescent period following his operation, he had become ill with the present illness. Four days prior to admission, he had noted malaise and increasing weakness. On the next day, the temperature was 103°F., and he suffered severe shaking and chills. During the next 48 hours, he became increasingly toxic, the temperature remaining between 101 and 103.6°F. He complained of severe headache. He was admitted to the Jewish Hospital on the 4th day of fever.

Thirty-seven years previously in Galicia, Poland, he had had an epidemic illness of several weeks' duration, with chills and fever. It is assumed that this was typhus, which was prevalent in eastern Europe at that time. He emigrated to the United States at the age of 19.

Physical examination showed a severely toxic patient whose condition resembled the so-called typhoidal state. The temperature was 102.8°F., the pulse 120, and the respirations 26. He was irritable and confused. The chest was clear except for transient rales at the right infrascapular area. The abdominal wounds in the right lower and left lower quadrant were indurated but showed no evidence of infection. Rectal examination was negative except for marked irritation around the anus.

Early the next morning, a discrete maculopapular rash was noted on the trunk. During the day, this spread to the back and the upper and lower extremities. It did not involve the palms or soles. The lesions blanched on pressure and were slightly pigmented. The patient remained febrile and toxic and complained of headache. In view of the history of a febrile illness in his native country and the sustained fever, chills, headache, mental state and rash, the diagnosis of Brill's disease was suggested.

On the morning of the 6th day of fever, after appropriate laboratory tests had been made, aureomycin was administered orally. That afternoon, the rash began to fade, and 24 hours after the administration of the drug, the skin was clear except for the axillary areas and the dorsa of the feet; within 48 hours, it had virtually disappeared. Twenty-four hours after the start of aureomycin, the patient was improved. His appetite was better, he was able to take some food, and his mental attitude changed. Because of the ileosigmoidostomy, camphorated tincture of opium was given to prevent the too rapid passage of the aureomycin through the bowel. Forty-eight hours after the beginning of specific therapy, on the 8th day, the temperature fell to normal and he was markedly improved. Improvement continued until discharge from the hospital on the 13th day.

Aureomycin was begun in doses of 250 mg. every hour for three doses and then every 2 hours until he became afebrile. The drug was continued every 4 hours for 24 hours and then for every 6 hours for 48 hours. He received a total of 10 gm. of aureomycin orally.

On admission the red-cell count was 4,100,000, with 12 gm. of hemoglobin, and the white-cell count was 9300, with 46 per cent neutrophils, 4 per cent monocytes and 10 per cent lymphocytes. There were 20 filamented and 80 nonfilamented forms. Urinalysis, the blood urea nitrogen and a blood culture were negative. Roentgenographic examination of the chest showed the lung fields to be normal. There was no evidence of metastasis or other tumor.

Capsules containing lice were implanted on this patient on the 6th day, and subsequent animal study was successful in isolating the rickettsias.

Agglutination tests for *E. typhosa* O and H, paratyphoid A, paratyphoid B, brucellosis and *P. OX-19* were negative on the 5th and 8th days of fever.

Complement-fixation tests with the specific antigens of epidemic and murine typhus were done at the Virus Diagnostic Research Laboratory of the Children's Hospital, Philadelphia. The results are presented in Table 3.

This patient had been convalescing at home after an operation and had no possibility of becoming infected by the vectors of typhus. The isolation of the causative rickettsia, together with the complement-fixation tests, indicated the diagnosis of Brill's disease.

TABLE 3. *Complement-Fixation Tests in Case 3.*

DAY OF TEST	EPIDEMIC-TYPHUS TITER	MURINE-TYPHUS TITER
6th	1:8	1:2
8th	1:128	1:8
13th	1:1024	1:256
20th	1:1024	1:128

DISCUSSION

It is to Brill[1-3] and Zinsser[4, 5] that the current concepts of this clinical entity are due. It had previously been assumed that this disease was related to the murine or endemic typhus described by Maxcy[6] as occurring in Mexico and the southeastern United States.

Between 1910 and 1933, in New York and Boston, 538 cases of Brill's disease were observed. About 95 per cent of these cases occurred in foreign-born persons, 93.6 per cent of whom had been born in the endemic typhus regions of Europe, with 80 per cent from Russia alone. About 90 per cent of the patients were Jewish. This preponderance is easily understood if one realizes that in that period immigration to this country consisted largely of the Jewish populations of the regions. It was also clear that patients in the second decade studied were about ten years older than those in the earlier group. None of the cases could be traced to the usual vectors, and it was shown that almost every patient was from a different home.

From bacteriologic studies, Zinssser ascertained that the virus of Brill's disease behaved like the European type. He concluded that a certain percentage of patients who have had typhus at an early age remain clinically well for years, but during this time are carriers of the disease and may later suffer a second attack. This variety of typhus is now named Brill's disease.

Blatteis[7] reported a series of 138 cases of this disease and confirmed Brill's observations. Ninety-five per cent of his patients were Jewish immigrants from Russia. None of the cases could be traced to exposure, and none of the hospital personnel contracted the disease, although no special precautions were taken. Lewis,[8] at the Pennsylvania Hospital, reported 13 cases with similar observations.

Morgan et al.[9] recently described 2 cases of Brill's disease occurring in Irish-born immigrants who had lived in Boston for over thirty years. The possibility of recent infection was ruled out so that the

disease probably represented the recrudescence of a previous infection.

During the recent war, new epidemics of typhus swept Europe and Asia. Troops operating in these areas were protected better than ever before by means of new insecticides, careful immunization and rigid quarantine of existing cases. In fact, during the recent war, Gordon[10] reports that only 3 confirmed cases of typhus occurred in the American troops in the European Theater of Operations. All experienced mild attacks. Two returned prisoners of war also were found to have typhus. Scoville[11] states that in the Japanese–Korean areas only 28 cases occurred in the occupation forces while an epidemic was raging in those countries. All patients had been vaccinated, and the disease was mild. No deaths resulted. It is surmised that some of the victims of these new epidemics may continue to harbor the organism, resulting in an increased incidence of Brill's disease years hence.

Aureomycin, an antibiotic derived from *Streptomyces aureofaciens*, holds promise of value in this and similar diseases. At the panel meeting of the New York Academy of Sciences held on July 21, 1948, the use of this drug was reported in rickettsial diseases of many types.

Wong and Cox[12] discussed the use of aureomycin in guinea-pig inoculations with *R. prowazeki*. When the drug was started before the febrile reaction to the inoculations had occurred, the fever was aborted. If the medication was begun after the onset of fever, the case was controlled in twenty-four to forty-eight hours, whereas the control animals had fever for approximately seven days.

Anigstein, Whitney and Beninson[13] confirmed this with similar studies using guinea pigs. Both oral and parenteral administrations of the drug were effective.

Schoenbach, Bryer and Long[14, 15] reported a case of Brill's disease in which therapy was started on the sixth day. Within forty-eight hours, the patient had become afebrile and asymptomatic.

In the study of a case of fever of undetermined origin, Brill's disease should be considered.

Fever, malaise, intense headache, chills, a skin rash and mental signs occurring in a foreign-born person years after his arrival from an area where epidemic typhus was present should cause one to consider this diagnosis. As previously noted by Schoenbach et al.[15] and again emphasized here, the Weil–Felix reaction cannot be used to exclude this disease. Agglutinations with the specific antigens of epidemic and murine typhus are necessary.

Confirmation of the diagnosis is made by serologic study and growth of the rickettsias on blood culture. Plotz[16] recently studied 23 cases of Brill's disease by means of complement-fixation tests. He found that the serums of the patients gave higher titers with the antigen of classic epidemic typhus than with that of murine typhus, thus lending additional support to Zinsser's hypothesis. Biopsy of skin lesions may also demonstrate the rickettsias.

Probably one of the reasons for failure to isolate the organism in Case 1 was that lice studies and the withdrawal of blood specimens were not started before the ninth day of the disease, and Murray[17] has found that the ninth day is too late in the course of Brill's disease to obtain the strain.

These 3 cases demonstrate clearly the value of aureomycin in Brill's disease. In Case 1, in which the patient was treated conservatively, spontaneous remission occurred on the eleventh day. In Case 2 aureomycin was begun on the eighth day, and remission occurred on the tenth day. In Case 3 the drug was started on the sixth day, and remission occurred on the eighth day. Early diagnosis with prompt administration of aureomycin leads to a dramatic remission within forty-eight hours.

Summary

Three cases of Brill's disease occurring in persons born in Russia, 2 of whom had a history of epidemic typhus years previously, are presented.

The patients were admitted with a diagnosis of fever of undetermined origin, and all the usual studies were negative.

The final diagnosis of Brill's disease was made by a careful history, serologic study and isolation of the organism.

Oral administration of aureomycin was used in the treatment of two cases with prompt clinical improvement.

We are indebted to Dr. Edward S. Murray, of the Army Epidemiological Board, working at the Laboratories of Harvard School of Public Health, who gave his time, efforts and advice in the special studies. Acknowledgment also is made to Dr. M. Michael Sigel, of the Virus Diagnostic Research Laboratory of the Children's Hospital of Philadelphia, who performed the complement-fixation tests in all 3 cases.

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ARTANE IN THE TREATMENT OF PARKINSON'S DISEASE

A Report of Its Effectiveness Alone and in Combination with Benadryl and Parpanit

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THIS report is a clinical evaluation of a recently synthesized drug called Artane‡ in 44 cases of Parkinson's disease. Artane is a piperidyl with the formula shown in Figure 1, on which also are written the structural formulas of Benadryl and Parpanit for comparison. These three chemicals are not similar in structure to either atropine or scopolamine.

The details of the chemical behavior and the pharmacologic and physiologic effects of the drug in animals are available in the reports of the manufacturer and will be published shortly. It is safe to use, has no serious side effects, is promptly eliminated and has no disturbing effects on the blood or the renal or cardiac system.

The hourly schedule chart devised by Viets and Schwab[1] and in use in the treatment of patients with myasthenia gravis is extremely valuable in the therapy of Parkinson's disease with the newer drugs.

By means of such a chart it is possible gradually to reduce the medication that the patient is taking when first seen and, at the same time, slowly to increase the dose of Artane. Sudden withdrawal of the antispasmodic effects of the atropine drugs is avoided by this means. A further advantage of such gradual overlapping of medication is the knowledge of the value in a particular patient of the two drugs together.

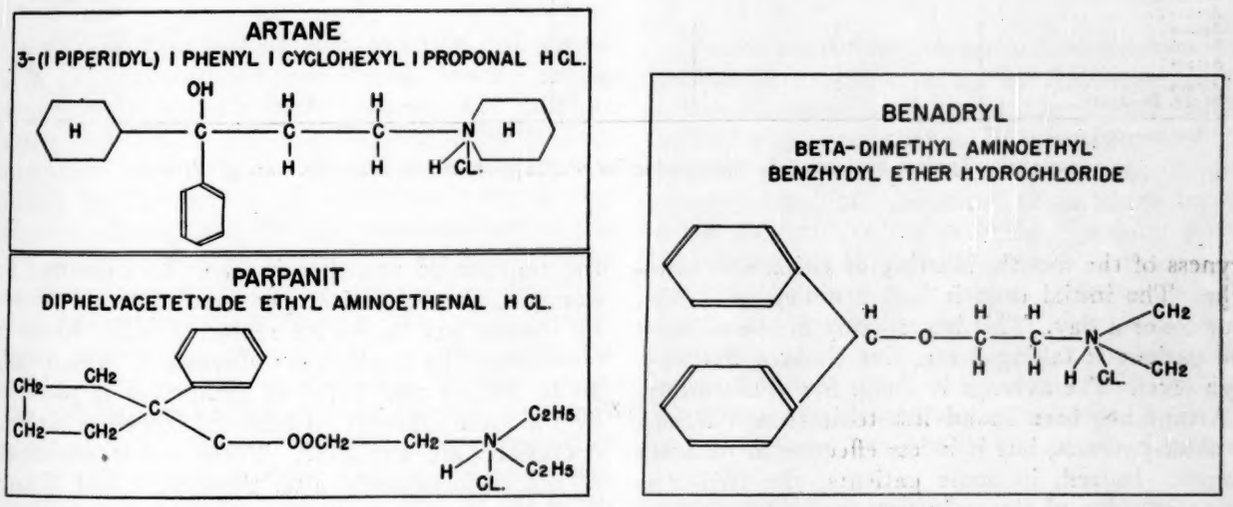

FIGURE 1. *Comparative Structural Formulas of Artane, Benadryl and Parpanit.*

An example of the regulation by slow reduction of the belladonna drug and increase in Artane is shown in Figure 2 and in the following case.

A 44-year-old woman with a history of severe influenza in 1919 and the onset of slowness in motion of the left arm 5 years before reporting for treatment had had involvement of the left leg and stiffness, fatigue and loss of fine movements in the fingers for 4 years. The tremor, first in the fingers and later in the wrist, had been present for 3½ years. For 1 year slight involvement in the right arm had been observed. The diagnosis of Parkinson's disease had been made at the onset by her family physician, and scopolamine, stramonium and amphetamine sulfate had been given in the usual doses.

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‡Supplies of Artane used in this investigation were furnished by the Lederle Company, Pearl River, New York.

For the past year she had been given Rabellon, 2 tablets four times a day. These belladonna drugs gave her some relief, but produced so much dryness of the mouth, blurred vision and depression of energy that she was thoroughly discouraged.

On the 3rd day of treatment with Artane the patient was relieved of her previously disturbing side effects, and noted a clear-cut increase in motor function, and the loss of fatigue. Rigidity was reduced, and there was a definite elevation of her mood and outlook. On the 7th day the 1½ tablets of Artane (3 mg.) produced a mild giddiness with blurred vision that was transient so that she went back to the 2-mg. dose every 3 hours according to the instructions given at her first visit.

When seen 2 weeks later she showed objectively less rigidity and tremor — more rapid movements in her fingers, better posture and was subjectively 50 per cent improved (toward her pre-illness status). Objectively by the various tests used she was 25 per cent better than on the belladonna drugs.

A month later, her improvement maintained, she was given Benadryl 50 mg. four times a day in addition to Artane, and when seen 6 weeks later she was 5 to 10 per cent better both objectively and subjectively than on Artane alone.

Artane is effective in different dosages in different patients. Overdosage produces side effects similar to those of Parpanit, such as giddiness, dryness of the mouth, blurring of vision and headache. The initial dose is half a tablet, or 1 mg., four times a day. This is gradually increased until the patient is taking 3 mg. five times a day as a high level. The average is 2 mg. five times a day.

Artane has been found less toxic than Parpanit in older patients, but it is less effective in reducing tremor. Indeed, in some patients, the tremor is worse in spite of the reduction in rigidity. Of 44 patients who had received Artane for over three months, only 7 (16 per cent) were relieved sufficiently, as compared to their status on atropine, to remain on Artane alone. Nine required the addition of Parpanit, and 7 were best regulated on a combination of Artane and Benadryl. Six others fared best on atropine drugs and Artane.

Twenty-nine, or 67 per cent, were 20 to 30 per cent better after such regulation on Artane than on the medication previously given. Seven were no better, and 8 could not tolerate Artane alone or in combination. Artane was therefore a failure in 33 per cent.

MASSACHUSETTS GENERAL HOSPITAL

Name N. B. Date 12/1/48 Unit No.

Medicine	a.m. 6	7	8	9	10	11	12	p.m. 1	2	3	4	5	6	7	8	9	10	11	12	12 m to 7 a.m.
Rabellon			2				2				2				2					Monday
Rabellon			2				1				2				1					Tuesday
Artane			½				½				½				½					Tuesday
Rabellon			1				1				1				1					Wednesday
Artane			½				1				½				1					Wednesday
Rabellon			1								1									Thursday
Artane			1				1				1				1					Thursday
Artane			1				1				1				1					Friday
Artane		1			1			1			1			1						Saturday
Artane		1			*1½			1			*1½			1						Sunday
Artane		1			1			1			1			1						Monday
Artane		1			1			1			1			1						2 wk. later
50 mg. Benadryl		1						1			1					1				2 wk. later

* = Overdosage.

FIGURE 2. *Typical Regulation by Slow Reduction of Parpanit and Gradual Increase of Artane.*

Discussion

In spite of the promising results of the newer belladonna preparations introduced from 1938 to 1942 such as Bulgarian belladonna root, Rabellon, Vinobel, Neoscopolamine and various mixtures, the treatment of Parkinson's disease has not been entirely satisfactory to the patient or the physician. The unpleasant and disturbing side effects, such as dryness of the mouth and blurred vision, occurred with all these compounds. In June, 1948, Budnitz[2] reported very favorable results with the antihistamine Benadryl, confirmed by Ryan and Wood.[3] In March, 1949, Schwab and Leigh[4] described success with a new synthetic drug, Parpanit. Neither of these substances produced the degree of drying of secretion or interference with accommodation encountered with atropine drugs.

The effectiveness of a treatment against the symptoms of a disease usually varies inversely with the number of remedies in use. In diabetes, for example, the 90 to 100 per cent success achieved by insulin has led to its replacing other forms of treatment. In Parkinson's disease, in which only 20 to 30 per cent relief of symptoms is possible, over a dozen different medications as well as surgical operation, are available. These newer chemicals do not, unfortunately, alter this deficit, and Artane is not in any sense an "insulin" for these chronic sufferers.

Since the relief of symptoms is only partial in Parkinson's disease, it is not an easy matter to draw accurate comparative results with the newer drugs and the older atropine mixtures. The course of the disease may be affected by spontaneous variation, rest in hospital, special attention, the influence of the observer on the patient, sedative effects, learning curves, enthusiasm of the observer, influence of new tests or drugs, favorable medical changes and effects of concomitant treatment. Greater accuracy may be obtained by objective as well as subjective reports, multiple points in

evaluation (ten points were used in the evaluation of these cases), large numbers of cases, placebo substitution, a long period of treatment, observation by different physicians (three different observers were involved in this investigation), different groups of patients (three separate groups were reported), adequate time on single drugs, a shift in drugs and multiple drugs and specific psychotherapy.

A truly efficient drug should be effective in any hands and not be subject to the individual aptitudes of the investigator. No such remedy is known today, and unless each patient is individually adjusted and frequently and carefully followed, with necessary alterations in dosage schedules, no better results will be obtained with these new compounds than with hyoscine alone.

The effectiveness of Benadryl as a remedy for the symptoms of Parkinson's disease has been confirmed, but the drug is less effective alone than either Parpanit or Artane (2 out of 9 cases). Benadryl in combination with Artane or Parpanit or even atropine drugs was effective in 12 of 24 cases in which it was tried.

The effect of other antihistaminic drugs, such as Thephorin, aminophylline and Benadryl mixture (Dramamine) is in the process of evaluation.

Summary

The effect of Artane alone and in combination with other drugs in alleviation of the symptoms of Parkinson's disease is reported in 44 cases. Favorable results were obtained in 67 per cent of cases in which treatment with Artane was given.

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ABDOMINAL PAIN IN HEMOCHROMATOSIS*

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AMONG the various manifestations of hemochromatosis are sometimes found certain symptomatic and objective features that simulate acute abdominal conditions. Writers in the medical literature in the United States have given scant notice to the finding of abdominal pain in this disease. Boland and Curran[1] presented one of the few reports of such abdominal symptomatology in hemochromatosis occurring in two brothers. The first entered the hospital with signs and symptoms suggesting cholecystitis. Cholecystectomy was performed, and on pathological examination the gall bladder was found to be normal. However, observation of a brown, cirrhotic liver at operation led to skin biopsy, and the diagnosis of hemochromatosis was made. The patient died on the ninth hospital day in hepatic coma. Later, his brother entered the hospital with similar symptoms. In view of the previous family history, laparotomy was not performed, and skin biopsy again revealed hemochromatosis. The patient recovered with the aid of symptomatic and supportive measures. Hurxthal[2] reported a case of hemochromatosis, proved by biopsy, that showed marked impairment of renal and adrenal function. Without comment he noted that about one week before admission the patient had had abdominal cramps and diarrhea.

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In contrast to the infrequency with which such findings have been reported by American authors is the statistical analysis of the French author Boulin,[3] who noted that in 70 cases 34 per cent of patients were originally admitted to the hospital because of painful abdominal crises, those located in the gall-bladder region being especially severe. He pointed out that these patients may even present pseudo-obstructive crises. Furthermore, he stated that spasm of the colon may at times be demonstrated by x-ray examination. In his general review Sheldon[4] cited an incidence of 6 per cent of patients who showed abdominal pain, 1 per cent having the symptoms with the onset of pigmentation.

Abdominal pain in itself is not an unusual feature of other types of liver cirrhosis, particularly during failure.[5,6] This pain is not usually associated with tenderness, however. Furthermore, its prognostic implications do not appear to be as immediately ominous as those in the cases presented below, in which the patients died soon after the onset of the abdominal symptoms.

Interest in this subject was stimulated on performance of the autopsy in Case 1. This patient entered the hospital with an abdominal picture that baffled both the medical and surgical services on which he was studied.

Examination of the Boston City Hospital records revealed that in the period between 1936 and 1946 there were 40 cases of hemochromatosis proved by autopsy at this hospital. Of these, abdominal pain was a prominent feature of the clinical course in 6. Three had demonstrable causes for the symptom, 1 had liver failure, 1 had a hepatoma, and 1 had a ruptured diverticulum with peritonitis. The remaining 3 had no morphologic background as a basis for the bizarre abdominal symptomatology. These cases are presented below.

Case Reports

Case 1. F. L., a 41-year-old man, had the diagnosis of diabetes mellitus made in October, 1945. Diet and insulin controlled the diabetes. A few weeks later he experienced upper abdominal pain, nausea and vomiting for 3 days. Several months later there was a recurrence of this pain, described as dull, continuous and nonradiating. On the evening of entry, there was an increase in the severity of the epigastric pain, without radiation. There was some nausea but no vomiting.

Physical examination revealed a well developed, middle-aged man in evident distress. The liver edge was half way between the costal margin and the umbilicus. The entire epigastrium was tender.

The blood pressure was 100/90. The temperature was 98°F., the pulse 114, and the respirations 20.

Laboratory work showed a yellow sugar reduction in the urine. The white-cell count was 14,400. The blood sugar was 265 mg. per 100 cc. The carbon dioxide combining power was 45 vol. per cent.

Treatment with parenteral injection of saline solution was inaugurated within the first 10 hours. The blood sugar values rose to 450 mg. per 100 cc., and during this period a total of 100 units of regular insulin was given. Ten hours after admission there was a green sugar reduction in the urine, but a + acetone test was noted for the first time. The blood chloride on the day after entry was 105 milliequiv. per liter (after 2300 cc. of saline solution had been given intravenously). The blood sugar fell to 130 mg. per 100 cc., and the carbon dioxide combining power to 38 vol. per cent. From the time of admission, a shock-like picture developed progressively in spite of plasma and saline administration. About 28 hours after entry the patient was treated for possible adrenal failure. Thirty cubic centimeters of adrenal cortical extract (Upjohn's aqueous extract) and 1500 cc. of 1.5 per cent saline solution were given. The patient rallied, and the blood pressure returned to audible limits at 80/60. No further cortical extract was obtainable, and he died 36 hours after admission.

Autopsy (46-57) revealed extensive hemochromatosis involving the liver, pancreas, heart, lungs, kidneys, spleen, bone marrow, lymph nodes, pituitary body and thyroid and adrenal glands. There was no morphologic explanation for the abdominal pain or sudden death.

Case 2. J. F., a 47-year-old man, entered the hospital in June, 1937, with pneumonia. Hepatomegaly and urinary findings indicative of diabetes mellitus were noted. The pneumonia cleared rapidly, and an insulin regimen was instituted. He left against advice 6 days after admission. In January, 1938, he returned for regulation of the insulin dosage. This was found to be quite difficult. Skin biopsy confirmed the suspicion of hemochromatosis. In May, 1938, the patient returned again with midabdominal, cramping pain of 4 days' duration.

Physical examination revealed a well developed, poorly nourished man in no acute distress. The liver extended one handbreadth below the costal margin. There was diffuse abdominal tenderness.

The blood pressure was 130/85, the temperature 98°F., the pulse 80, and the respirations 20.

Laboratory studies showed a green sugar reduction in the urine in addition to a trace of albumin and a + test for bile. The red-cell count was 3,750,000 and the white-cell count was 7200. Blood chemical studies revealed a fasting blood sugar of 267 mg. per 100 cc.

The patient showed signs of progressive cardiac decompensation and transitory episodes of fibrillation. On digitalis, ammonium chloride and fluid restriction he made rapid improvement and left against advice 2½ weeks after admission. Within 2 weeks he was readmitted with evidence of dehydration and diabetic coma. He died within 36 hours in spite of vigorous supportive measures.

Autopsy (38-316) showed marked hepatomegaly and evidence of hemochromatosis in the liver, kidney, pancreas and heart.

Case 3. W. T., a 58-year-old man, entered the hospital in April, 1933, with signs and symptoms of scurvy, for which he was treated successfully. In September, 1939, he returned with signs of congestive failure. Four months before his final admission, he returned again with cardiac decompensation, when a diagnosis of arteriosclerotic heart disease with auricular fibrillation was made. The last admission, on February 23, 1945, was again because of cardiac decompensation.

Physical examination showed a middle-aged man in acute distress with orthopnea and dyspnea. There were crackling rales and dullness at the lung bases. The liver edge was palpated four fingerbreadths below the costal margin. Pitting edema of the legs was evident. Slight scleral icterus was noted.

The blood pressure was 112/76. The temperature was 98°F., the pulse 120, and the respirations 26.

Examination of the urine revealed a ++ to ++++ test for albumin and a + to ++ test for bile, and the sediment contained occasional red and white cells. The nonprotein nitrogen was 44 mg., and the fasting blood sugar 115 mg. per 100 cc. Studies of liver function demonstrated impairment.

The patient was treated with digitalis, a salt-free diet and ammonium chloride. On this regimen he became asymptomatic and was allowed out of bed on the 4th day. On the 12th hospital day he suddenly complained of abdominal pain and went into a state of peripheral vascular collapse. Twelve hours later he had a similar attack of pain and died. The clinical impression was pulmonary infarction.

Autopsy (45-127), performed 5 hours post mortem, showed arteriosclerotic heart disease, rheumatic heart disease with involvement of the aortic valve, and hemochromatosis involving the heart, lungs, liver, spleen, pancreas, kidneys, gastrointestinal tract, lymph nodes, thyroid, adrenal and parathyroid glands, testes, bone marrow, skin and pituitary body. There was no demonstrable morphologic cause for the pain or sudden death.

Discussion

Many hypotheses can be offered as reasons for these symptoms. One of the most attractive possibilities to account for the episodes of abdominal pain in hemochromatosis is adrenal cortical insufficiency. This symptom, according to Soffer,[7] occurs in a relatively small percentage of patients with Addison's disease in the intercritical period, but crises are often heralded by gastrointestinal manifestations, including abdominal pain. Adrenal involvement as one of the multiple endocrinopathies of hemochromatosis seems well established.[3, 4, 8] Hurxthal's[2] case is an example. The patient of Layani,[9] a twenty-nine-year-old man whose pigmentation cleared on massive doses of vitamin C, is possibly another. A relation has been shown between adrenal cortical extracts and vitamin C,[10] and between vitamin C and secretion of adrenal cortical hormones under stress.[11-13] Moreover, the first case reported above suggested a therapeutically diagnostic response to the adrenal cortical extract administered. Evidence of the same nature is afforded by the report of Oumansky and Longuet[14] in an eighteen-year-old girl with

hemochromatosis whose signs of heart failure disappeared with cortin therapy. Indeed, in the early phases hemochromatosis is most often confused with Addison's disease.[3, 15] The appearance of diabetes mellitus is a major aid in pointing to the true disease, for primary adrenal insufficiency is extremely rarely associated with diabetes.[16]

Since the death of these patients in congestive failure caused by extensive deposition of hemosiderin in the myocardium is now a recognized entity,[17, 18] pain due to passive congestion in abdominal viscera is a possibility. Hemosiderin deposition may also result in abnormalities in cardiac rhythm,[19] making the patients candidates for embolic phenomena.

Liver failure per se may be the cause of severe abdominal pain.[20] However, this is one of the unusual manifestations of this rare disease.

Pancreatitis must also be considered in the differential diagnosis of abdominal pain. In the cases reported above, however, there was no pathological evidence that the pancreas was the cause of the symptoms.

Other painful manifestations of hemochromatosis, such as pain in the extremities,[21] precordial episodes simulating myocardial infarction but without morphologic findings at post-mortem examination[15] and spasm of the large bowel,[3] suggest a common etiology in isolated episodes of vasospasm or colic, owing to the immediate effects of hemofuscin deposition in smooth-muscle cells of arteries and of the alimentary tract.[22]

Finally, pain in the abdomen in this disease may be a manifestation of abnormalities in glucose metabolism. In hypoglycemia, abdominal pain is possibly due to parasympathetic activity manifested by increased contraction of various segments of the gastrointestinal or biliary tract.[23] Ketosis, which may also be accompanied by acute abdominal pain, tenderness, nausea and vomiting, may be an especially dangerous pitfall because of the often associated abdominal muscular rigidity, leukocytosis and fever.[23] In diabetes as difficult to control as that of hemochromatosis, hypoglycemia and ketosis are perennial threats.[24, 25]

Summary

Attention is called to a clinical syndrome of abdominal pain in hemochromatosis that has been mentioned very rarely in the medical literature in the United States.

Three autopsied cases showing no morphologic basis for the abdominal episodes are reported.

Several possible explanations of this syndrome are presented.

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MEDICAL PROGRESS

LABORATORY DATA IN CLINICAL MEDICINE: UNITS OF MEASURE, COSTS, AND QUANTITATIVE SIGNIFICANCE OF RESULTS*

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THE potential number and cost of laboratory examinations in clinical medicine are enormous. Accordingly, it is a considerable responsibility for the physician to choose wisely the laboratory procedures that are to be performed. Certain tests have become "routine" because they have proved to give basic information rapidly and inexpensively in the *screening* of a large number of systems of the body for detecting the presence of disease. These procedures include the determination of the hematocrit (or hemoglobin), white-cell count and differential white-cell count, analysis of urine, inspection of the stool, examination for occult blood and serologic test for syphilis. As will be discussed in a separate communication, the red-cell count is not recommended as a routine screening procedure.

The choice of laboratory examinations is usually based on symptoms, signs or laboratory data that

TABLE 1. *Selected Units of Measure from the Metric System, and Relations among Them.*

UNIT			ABBREVIATION
Prefixes:			
deci-	one-tenth, 1/10, 0.1, 10^{-1}		(d)
centi-	one-hundredth, 1/100, 0.01, 10^{-2}		(c)
milli-	one-thousandth, 1/1000, 0.001, 10^{-3}		(m)
micro-	one-millionth, 1/1,000,000, 0.000001, 10^{-6}		(μ)*
Units of length:			
1 meter (m)	= 10 decimeters (dm)	= 100 centimeters	(cm)
1 centimeter (cm)	= 10^{-2} m	= 10 millimeters	(mm)
1 millimeter (mm)	= 10^{-3} m = 10^{-1} cm	= 1000 microns	(μ)
1 micron (μ)*	= 10^{-6} m = 10^{-4} cm	= 1000 millimicrons	(mμ)
1 millimicron (mμ)	= 10^{-9} m = 10^{-7} cm	= 10 angstroms	(A)
1 angstrom (A)	= 10^{-10} m = 10^{-8} cm	= 100 micromicrons	($\mu\mu$)
1 micromicron ($\mu\mu$)	= 10^{-12} m = 10^{-10} cm		
Units of area:			
1 square meter (m^2)		= 10,000 square centimeters	(cm^2)
1 square centimeter (cm^2)		= 100 square millimeters	(mm^2)
1 square millimeter (mm^2)			
Units of volume†:			
1 cubic meter (m^3)	$\approx$	1,000,000 milliliters	(ml)†
1 liter (L)	=	1,000 milliliters	(ml)
	$\approx$	1,000 cubic centimeters	(cm^3)†
1 milliliter (ml)	$\approx$	1 cubic centimeter	(cm^3)†
	$\approx$	1,000 cubic millimeters	(mm^3)†
1 cubic millimeter (mm^3)	=	1,000 cubic microns	(μ^3)
1 cubic micron (μ^3)			
Units of mass:			
1 kilogram (kg)	=	1,000 grams	(gm)
1 gram (gm)	=	1,000 milligrams	(mg)
1 milligram (mg) = 10^{-3} gm	=	1,000 micrograms	(μg)
1 microgram (μg)‡ = 10^{-6} gm	=	1,000,000 micromicrograms	($\mu\mu$g)
1 micromicrogram ($\mu\mu$g)‡ = 10^{-12} gm			
Units of concentration:			
1 mole per liter (M/L) = M_m gm in 1 L (see footnote§)			
1 millimole per liter (mM/L) = 1/1000 M/L = 10^{-3} M/L			
1 equivalent per liter (eq/L) = M_a gm/valence in 1 L = 10^{-3} eq/L (see footnote§ and Table 2).			
1 milliequivalent per liter (meq/L) = 1/1000 equivalent per liter = 10^{-3} eq/L			
1 gram per liter (gm/L) = 1,000 milligrams per liter (mg/L)			
1 milligram per liter (mg/L) = 10^{-3} gm/L = 1000 micrograms per liter (μg/L)			
1 microgram per liter (μg/L) = 10^{-6} gm/L = 1,000,000 micromicrograms per liter ($\mu\mu$g/L)			
1 micromicrogram per liter ($\mu\mu$g/L) = 10^{-12} gm/L			

*μ is the Greek letter mu. When used alone it means 1 micron; when used as a prefix it means micro-.

†Note that some of these relations are only approximate; these are indicated by the sign $\approx$. True equality is indicated by the sign =. Note that 1 liter is exactly equal to 1000 ml but not exactly equal to 1000 cm^3 (see text). The abbreviation cm^3 replaces cc.

‡The terms gamma (γ), for microgram, and gamma gamma ($\gamma\gamma$), for micromicrogram, have been used, but are not recommended since they add confusion and offer no advantage over the standard nomenclature, in which μ (mu) indicates one millionth of a meter (micron), μg indicates one microgram (millionth of a gram), and $\mu\mu$g indicates one micromicrogram (one million-millionth of a gram).

§Note that molecular weight M_m and atomic weight M_a are both pure numbers; see Table 2 for examples using the atomic weight of electrolytes. In physical chemistry molal solutions are used; a molal solution contains 1 gram molecular weight (M_m gm) of solute, dissolved in 1000 gm (*not* ml) of solvent. Thus, a 0.2 molal solution contains 0.2 M_m gm of solute per 1000 gm of solvent.

*Adapted from *A Syllabus of Laboratory Examinations in Clinical Diagnosis* (in press), by permission of the Harvard University Press.

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indicate a presumptive value for the performance of a particular test or group of tests. The use of each laboratory test is based on a knowledge, first, of the clinical indication for performing the test, the nature of the test and the diagnostic significance of the results. Three particular aspects of laboratory examinations are considered in the material presented below — namely, certain units of measure of clinical data, the cost to the patient and the degree of accuracy that is required of a laboratory procedure so that the results may be significant in establishing an aspect of the diagnosis or treatment.

TABLE 2. *Normal Values for Electrolytes of Human Serum and Plasma Expressed in Milligrams per 100 ml and Converted to Milliequivalents per Liter, as Modified from Gamble.*[1]

ION	NORMAL VALUES*	ATOMIC WEIGHT	VALENCE	CONVERSION OF CONCENTRATION C IN MG/100 ML TO MEQ/L		NORMAL VALUE
				FORMULA	FACTOR	
	(mg/100 ml)	M_a	V	$(C \times 10/M_a) V$		(meq/L)
Cations						
$Na+$	313–333	23	1	$(C \times 10/23) \times 1$	= 0.435	136–145
$K+$	14–19	39	1	$(C \times 10/39) \times 1$	= 0.257	3.5–5.0
$Ca++$	9.0–10.5	40	2	$(C \times 10/40) \times 2$	= 0.5	4.5–5.3
$Mg++$	1.2–2.4	24	2	$(C \times 10/24) \times 2$	= 0.833	1–2
Total						145–157
Anions						
HCO_3- (CO_2/vol %)	58.0–62			1/2.22†	= 0.455	26–28
$Cl-$	349–371	35	1	$(C \times 10/35) \times 1$	= 0.286	100–106
$H_2PO_4=$ (mgP)	3.0–4.5	31	1.8‡	$(C \times 10/31) \times 1.8$	= 0.58	2–3
$SO_4=$ (mgS)	1.6–2.4	31	2	$(C \times 10/32) \times 2$	= 0.625	1.0–1.5
Protein (gm/100 ml)	6.5–8.0				2.43§	16–19
Total						145–157

*Normal values for blood, plasma and serum.[2]

†1 millimole per liter (or 1 milliequivalent per liter) of CO_2 under standard conditions (760 mm-of-mercury and 0°C) occupies 22.26 ml; or 1 milliequivalent per *100 ml* occupies 2.22 ml. Therefore, the content (volume) of CO_2 in milliliters per 100 ml of serum (CO_2/volume per cent), when divided by 2.22 gives CO_2 in milliequivalents per liter.

‡As stated by Gamble,[1] the valence of HPO_4 is taken as 1.8 because at the normal pH of extracellular fluid, 20 per cent of the concentration of this radical carries 1 equivalent of base (BH_2PO_4), and 80 per cent 2 equivalents (B_2HPO_4), B representing univalent base. Base equivalence per unit of (HPO_4) is therefore 0.2 + (0.8 x 2) = 1.8. The double valency sign is this small extent inaccurate.

§Derived by titration of the base that is bound by proteins of norma serum at pH 7.35.[3]

CERTAIN UNITS OF MEASURE (METRIC SYSTEM)

The physician is called upon to interpret data expressed in units of measure that vary greatly in magnitude. Thus, a patient weighing 70 kg may have a blood volume of 5 liters, a nonprotein nitrogen of 20 mg per 100 milliliters of blood, a blood sodium of 140 milliequivalents per liter, a serum iodine (protein bound) of 4 micrograms per 100 milliliters and a mean corpuscular hemoglobin (for the red cells) of 30 micromicrograms. The shift from micromicrograms to kilograms or from milliequivalents per liter to milligrams per 100 milliliters frequently results in confusion. In Table 1, the usual units of measure in the metric system are arranged in descending order of magnitude, with their abbreviations* and equivalents.

The writing of large or small numbers is facilitated by the use of powers of ten. Thus, 1,000,000 = 10^6; 1034 = 1.034×10^3. A negative exponent indicates a reciprocal; $10^{-3} = 1/10^3 = 1/1000 = 0.001$; $2.65 \times 10^{-6} = 2.65 \times 0.000001 = 0.00000265$. The red-cell count in millions per cubic millimeter may be expressed, for example, as $5.34 \times 10^6/mm^3$; the white-cell count in thousands per cubic millimeter may be expressed, for example, as $8.23 \times 10^3/mm^3$ (see Table 6).

Expression of the concentration of *electrolytes* of plasma, serum and extracellular fluids has caused confusion. Ions are usually expressed in terms of their chemical equivalence, by the statement of their concentration in milliequivalents per liter, rather than in milligrams or grams per 100 ml. As shown in Tables 1 and 2, the conversion to milliequivalents per liter, for the individual ions, is given by the formula

$$\text{Concentration (meq/L)} = \frac{\text{Concentration (mg/100 ml)} \times 10}{M_a} \times V,$$

where V is the valence and M_a is the atomic weight. The normal values and the formulas for conversion to milliequivalents per liter are shown in Table 2.

It may be remarked that the *unit of volume* used in chemical and biologic work is the *liter*, which is the volume of 1 kg of pure water at the temperature of maximum density, 4°C, and under a pressure equivalent to 760 mm of mercury. It was intended by the constructors of the metric system that the kilogram should be the mass of 1 cubic decimeter (10^{-3} m^3) of pure water under these conditions of temperature and pressure, but later, more accurate measurements showed that they had made an error, and the kilogram is now taken as the mass of the international prototype kilogram, a block of metal kept at the International Bureau of Weights

*It will be noted that periods and other punctuations are not used after any abbreviation, following the practice of the *Handbook of Chemistry and Physics*. Thirtieth edition. Cleveland: Chemical Rubber Publishing Co., 1948. Pp. 2637-2649. Also, the abbreviation of gram or grams is taken as (gm) rather than (gms.); similarly, milligram or milligrams is abbreviated (mg) rather than (mgm.) or (mgms).

TABLE 3. *Examples of Charges Made for Certain Laboratory Examinations (1949).*

EXAMINATION	CHARGES BY FOUR DIFFERENT HOSPITALS* (1) $	(2) $	(3) $	(4) $
Hematology:				
White-cell count	2.00	1.00	1.00	1.00
White-cell count and differential	3.00	2.00	2.00	2.50
Complete blood count	5.50	4.00	4.00	4.00
Anemia unit: Complete blood count, hematocrit, hemoglobin, MCV, MCHC, MCH, reticulocyte count			2.00† or 6.00†	5.00
Platelet or reticulocyte count	3.00	2.00	2.00	2.00
Examination for malarial parasites	3.00	3.00	2.00	2.00
Hematocrit	1.00	2.00	1.50	1.50
Osmotic fragility of red cells			5.00	7.00
Sedimentation rate	2.00	2.00	2.00	2.00
Bleeding time, coagulation time, platelet count	2.00	4.50	3.00	4.00
Prothrombin time	2.50	2.00	3.00	3.00
Hemorrhagic disease unit: bleeding time, clotting time, clot retraction, platelet count, prothrombin time			5.00	8.00
Blood grouping: ABO	2.50			2.00
Blood grouping: ABO and Rh	5.00	2.00	3.00	2.50
Rh grouping	2.50	2.00		
Cross matching	2.50			
Blood chemistry:				
Sugar	5.00	2.00	3.00	3.00
Glucose tolerance test	15.00	5.00	7.50	2.50‡
Urea nitrogen or nonprotein nitrogen	5.00	3.00	3.00	4.00
Chloride	5.00	2.00	2.00	4.50
Total protein, copper sulfate method	2.50			6.00
Albumin and globulin concentrations	10.00	7.00	5.00	9.50
Cholesterol	5.00	3.00	4.00	6.00
Icteric index	2.50		1.00	1.50
Bilirubin, direct and indirect	5.00	3.00	3.00	4.00
Bromsulfalein test	2.50	3.00	3.00	2.00
Uric acid	5.00	3.00	4.00	4.00
Creatinine	5.00	2.00	3.00	2.00
Sodium		3.00	10.00	4.00
Calcium	5.00	4.00	5.00	6.50
Phosphorus	5.00	2.00	3.00	4.00
Phosphatase (alkaline)	5.00	5.00	5.00	5.00
Calcium, phosphorus and phosphatase	10.00			13.50
Acid phosphatase	5.00	5.00	5.00	5.00
Carbon dioxide combining power	10.00	2.00	4.00	4.00
Liver-function tests:				
Serum bilirubin, quantitative urobilinogen in the urine, bromsulfalein, cephalin flocculation, thymol turbidity, alkaline phosphatase and serum protein with albumin and globulin			12.00	15.00
Urinalysis:				
Urinalysis (specific gravity, pH, color, proteins, sugar, sediment)	1.50	1.00	1.00	1.50
Quantitative sugar	3.00	1.00	1.00	1.50
Phenolsulfonephthalein	3.00	2.00	2.00	1.50
Urobilinogen, 2 hr. sample		1.00		4.00
Renal-function unit: nonprotein nitrogen, concentration test (Fishberg), phenolsulfonephthalein (intravenous)			3.00	
Urea clearance		7.50	7.50	10.00
Feces:				
Inspection, test for occult blood, screening for parasites	2.00	3.00	3.00	1.50
Examination for parasites and ova	5.00	5.00	2.00	1.50
Quantitative fat		5.00	7.50	
Urobilinogen, qualitative		1.00	1.00	1.00
Spinal fluid:				
White-cell count	1.50			1.50
Test for globulins	1.00			1.50
Total protein	3.00	7.50	7.00	2.50
Gold-sol curve	5.00			2.50
Wassermann	5.00			8.00
Spinal-fluid complete: smear, culture, white-cell count, differential, qualitative protein	5.00	5.00	5.00	
Gastric analysis:				
Miscellaneous:				
*Frozen section, consultation			25.00	20.00
Electrocardiogram (usual leads)	7.50	7.50	10.00	10.00
Electrocardiogram (16 leads)	15.00	20.00		
Basal metabolism	7.50	5.00	7.50	9.00
				4.00§
Friedman or Aschheim-Zondek test for pregnancy	7.50	5.00	9.00	8.00
Test for follicle-stimulating hormone		7.50		10.00
Test for 17-ketosteroids		5.00		10.00
Blood culture	6.00	5.00	3.00	13.50
Inoculation of guinea pig for tuberculosis	10.00	7.50		13.50
Sputum for tubercle bacilli	6.00	2.00		2.50
Papanicolaou smear		3.00		6.50
Blood Wassermann (rapid test)	5.00	3.00	4.00	2.50
Antibiotic sensitivity	5.00	5.00		7.00 one
				10.00 two
X-ray:				
Chest, stereo (with fluoroscopy)	15.00	15.00	15.00	15.00
Gastrointestinal series with 6-hr film	25.00	15.00	25.00	15.00
Barium enema	15.00	15.00	17.50	20.00
Gall-bladder test	15.00	10.00	20.00	20.00
Intravenous pyelogram	25.00	15.00	25.00	15.00
Retrograde pyelogram		15.00	20.00	15.00
Bone series	25.00		10.00	
Skull, anterior, posterior, lateral		10.00	20.00	20.00
Ventriculogram		15.00		15.00
Maximum charge for all laboratory examinations		50.00		

* (1) Stanford University Hospitals, San Francisco, California (rates for private patients).
(2) Baker Memorial, Massachusetts General Hospital, Boston, Massachusetts. Maximum charge for total laboratory fees, $50.00 (rates for private patients).
(3) Faulkner Hospital, Boston, Massachusetts (rates for private patients).
(4) A teaching hospital in Philadelphia, Pennsylvania (rates for semiprivate patients).

†Complete blood count included in routine charge for inpatients. The charge of $6 is for an outpatient.

‡For each determination.

§Repeat test.

and Measures near Paris; it is equal to the mass of 0.001000027 m^3 (= 1.000027 dm^3) of water. Consequently, 1 ml = 1.000027 cm^3, but the *mass of 1 ml of pure water under the conditions specified is exactly 1 gm.* For these reasons the *milliliter* (ml) is substituted for the more familiar cubic centimeter (cm^3)* as a unit of volume.

For convenience and clarity in expression, units that avoid the use of large numbers or large fractions are chosen when possible. For example, a patient's weight of 70,000 gm is expressed as 70 kg; a dosage of vitamin B_{12} is more conveniently expressed as 15 μg (micrograms) than 0.015 mg or 0.000015 gm or 15 x 10^{-6} gm; a concentration of potassium in the serum is expressed as 5 milliequivalents per liter (meq/L) rather than 0.005 equivalent per liter (eq/L). The expression "milligrams per cent (mg %)" has caused confusion since, literally, it means the number of milligrams per 100 parts — that is, per 100 mg — and not per 100 cm^3 or per 100 ml, as is usually implied. Accordingly, the expression "milligrams per cent" should be *abandoned*, and units that are determinate should be used, such as mg/100 ml or mg/L. Thus, the concentration of nonprotein nitrogen in whole blood is expressed as 30 mg/100 ml, rather than 0.03 gm/100 ml and not as 30 mg %.

Current Cost of Laboratory Examinations and Certain Laboratory Apparatus

Unfortunately, laboratory examinations cost money because of the time, skill, reagents, apparatus, and building space required for their proper performance. The increasing number and cost of laboratory procedures required for proper diagnosis and treatment presents a significant economic problem in the care of the patient. There is no doubt that well controlled laboratory examinations are essential, but because they are expensive, they should be ordered with care, done with proper accuracy and interpreted critically. Laboratory examinations are obviously subject to abuses. It may be improper for a patient to pay for extra laboratory examinations that are performed primarily for teaching or research purposes. A more serious error may result from the failure to perform the proper kind or number of tests because of cost to the patient. It is probably essential that the patient be instructed in the need, cost and value of laboratory examinations in his particular case, just as he is informed of the need, cost, and value of treatment with an antibiotic or by an operative procedure.

No figures are available on the true costs of laboratory procedures. In place of a cost analysis, the current charges made for certain laboratory tests in different parts of the country are listed in Table 3. At one hospital (No. 3 in Table 3) for private patients, a flat laboratory fee is charged to each patient to cover routine laboratory work required of all who are admitted. Since the routine varies on different services, the fees charged are as follows: medical patients, $9.00; surgical patients, $6.00; obstetric patients, $4.00. The charges cover blood counts, urinalysis and certain other procedures. Other tests are charged for separately (see column 3, Table 3). All charges are based on a unit system, in which each unit is valued at $0.50, as recommended by the New England Pathological Society in unpublished data.

*The cubic centimeter, as with other volumes expressed as the cube, is abbreviated as (cm^3) rather than the more familiar (cc).

Table 4. *Equipment Used for Clinical Laboratory Procedures.*

Items	Unit Price (1949) $
Monocular microscope with oil-immersion objective (complete)	299.00
Test tubes and holders*:	
Test tubes, 20 x 150 mm	0.07
Centrifuge tube, 15 ml, soft glass, ungraduated	0.10
Centrifuge tube, 15 ml, graduated	0.86
Centrifuge tube, 15 ml, Addis or Shevky-Stafford	1.54
Test tube brush	0.07
Test tube holder, wire	0.12
Test tube rack	1.20
Pipettes*:	
10 ml, Mohr	0.97
1 ml, serological	0.75
0.10 ml, micro for Folin sugar method	1.00
0.02 ml, for Sahli hemoglobinometer	1.00
Hematocrit pipette with rubber bulb	0.30
Vessels*:	
Cylinder, 50 ml, graduated	1.10
Beaker, 250 ml, pyrex	0.25
Flask, Erlenmeyer, 250 ml, pyrex	0.32
Evaporating dish, porcelain	1.50
Wine glass	0.40
Screw cap jar	0.15
Urinometer: 50 ml cylinder, ungraduated hydrometer	0.80 0.61
Funnel, 2½ in. diameter	0.40
Dropping bottle, rubber bulb	0.10
Ironware*:	
Tripod	0.84
Wire gauze with asbestos, 5 in	0.12
Bunsen burner	0.57
Clinical model centrifuge (International Equipment Company)	105.00
Hemoglobinometry:	
Tallqvist hemoglobin scale (book)	1.00
Sahli (Hellegi hemoglobinometer)	18.00
Haden-Hauser (clinical model)	19.05
Spencer hemoglobinometer (American Optical Company). Transformer	38.00 15.00
Evelyn, macro-photoelectric cell colorimeter (complete)	385.00
Klett-Summerson photoelectric cell colorimeter	171.00
Wintrobe tubes*	1.10
Water bath, constant temperature (37°-60° C), with racks	100.00
Syringes, needles and carriers*:	
10 ml	3.25
30 ml	4.80
50 ml	7.00
Syringe carriers	0.50
Hypodermic needles, 19 gage	0.25
Hypodermic needles, 20 gage	0.23
Hypodermic needles, 22 gage	0.23
Blood trays*	5.00
Sedimentation racks, Wintrobe method	10.00
Sedimentation rack, Westergren, 6 tube	16.50
Tubes, sedimentation, Westergren	0.97
Comparator block and icteric index standards	12.60

*Unit prices given apply when items are purchased in lots of 1 dozen.

Certain tests have been grouped together into *units* such as those related to anemia, hemorrhagic disease, liver function and kidney function. In these instances, charges are kept to a minimum and scaled to the patient's income to encourage the use of these groups of procedures in diagnosis.

The cost of equipment necessary for performing certain of the basic clinical laboratory examinations is listed in Table 4.

Quantitative Evaluation of Data

With the enormous increase in the number of laboratory examinations that can be made, the physician is called upon continuously to evaluate data in a scientific manner — that is, to know the limits of significance of the results quantitatively and clinically. Quite properly, the physician wishes to obtain a maximum of reliable information on which to base a diagnosis, and to obtain it at minimum cost in minimum time and as simply as possible. Accordingly, there will always be a high priority in clinical medicine for the development of *screening examinations* that will indicate the presence or absence of disease in a rapid, reliable and inexpensive manner. The data required may be qualitative, semiquantitative or, in certain instances, precisely quantitative to be of proper use to the physician in diagnosis and treatment. Again, the physician balances the potential value of a test against its cost, but gives first priority to the clinical indication for the procedure.

In general, costs rise with the degree of accuracy required, since precision usually requires more time of highly skilled personnel* and more equipment than qualitative or semiquantitative examinations. Accordingly, the physician will be alert to know the degree of accuracy required and to interpret data with a full knowledge of their limitations in specificity and limits of error. For example, the determination of plasma fibrinogen, serum albumin and serum globulin requires skill in the use of the Kjeldahl method of nitrogen analysis; these determinations inevitably are expensive. If the procedures are done by unskilled workers, the data are erroneous, not reproducible and so misleading clinically as to be useless and treacherous (see Fig. 1 for serum albumin). Accordingly, certain screening examinations for plasma proteins that are rapid, inexpensive and semiquantitative have an important place as diagnostic procedures. For example, if the total protein is normal as measured by the copper sulfate method, if the serum globulins are normal as indicated by the formol-gel reaction and if the plasma fibrinogen and serum globulins are normal as indicated by the sedimentation rate, plasma protein fractions may be considered normal, and its quantitative determination is not essential for diagnosis.

It is emphasized, immediately, that it may be as fallacious and wasteful to use a refined quantitative procedure when qualitative results suffice as it is to attempt the evaluation of data of qualitative significance when precise information is necessary. Accordingly, a knowledge of the limits of accuracy of the data is an integral part of their diagnostic evaluation. There is no place in medicine for blind faith in a written figure on a patient's chart. Listed below are examples of the wide span of the limits of accuracy of data as applied to diagnosis and treatment.

*Fortunately, there are occasional exceptions. For example, the hematocrit can be determined with remarkable accuracy and in a short time by a trained high-school girl equipped with a centrifuge and a dozen Wintrobe tubes. This easy precision results from the admirable features of the method itself. Conversely, the red-cell count, as a method, has an inherent error of chance distribution of cells that requires long labor and great care to overcome (see Table 6).

Qualitative Determinations

An unrefined, and possibly nonspecific, qualitative procedure is frequently of great *value* as a screening procedure or as a true diagnostic method. Thus, the presence of gross blood in urine, feces, vomitus or sputum may require only visual observation for detection, and certainly does not require refined quantitative evaluation to be of important diagnostic value. Similarly, if a patient's vomitus produces a bright-red color with the pH indicator, Töpfer's reagent, this is first-class evidence for the presence of free hydrochloric acid and would immediately exclude a diagnosis of classic Addisonian pernicious anemia. If a patient bleeds indefinitely after an ordinary capillary puncture for the collection of blood, this observation is as eloquent data as may be obtained from a test performed especially for measuring the bleeding time. If the urine becomes solidified when boiled with acetic acid, this test alone requires a presumptive diagnosis of nephrosis. If the hematocrit tube shows a layer of white cells that is 10 mm high, the presumptive diagnosis is leukemia until proved otherwise. If a patient enters the hospital with manifest history and signs of dehydration, the observation that the specific gravity of the urine sample is only 1.010 suggests low concentrating power and abnormal renal function. The passage of a stone into urine or stool is a reliable qualitative datum.

However, qualitative determinations have inevitable *limitations* that require full recognition. For example, the observation of blood in the vomitus, without further information concerning the patient, may not indicate whether the bleeding is of minor nature or of a magnitude that threatens the life of the patient. The passage of a stone in the urine does not in itself indicate whether the patient has such an abnormality as a parathyroid tumor, excessive ingestion of alkali or a congenital defect in the metabolism of cystine.

Semiquantitative Determinations

Data of semiquantitative accuracy are frequently as *valuable* as more refined information. This is evidenced by the enormous number of tests, reported in terms of degree of positivity, and expressed as "positive or negative" or positive in terms of "+to 4+." For example, in a patient with known diabetes, a "brick red" (4+) test with Benedict's qualitative sugar reagent is reliable semiquantitative information, as is a 4+ reaction for acetone bodies. There may be no requirement, in the proper handling of diabetic coma, to determine, in a more quantitative manner, the sugar and acetone bodies in the

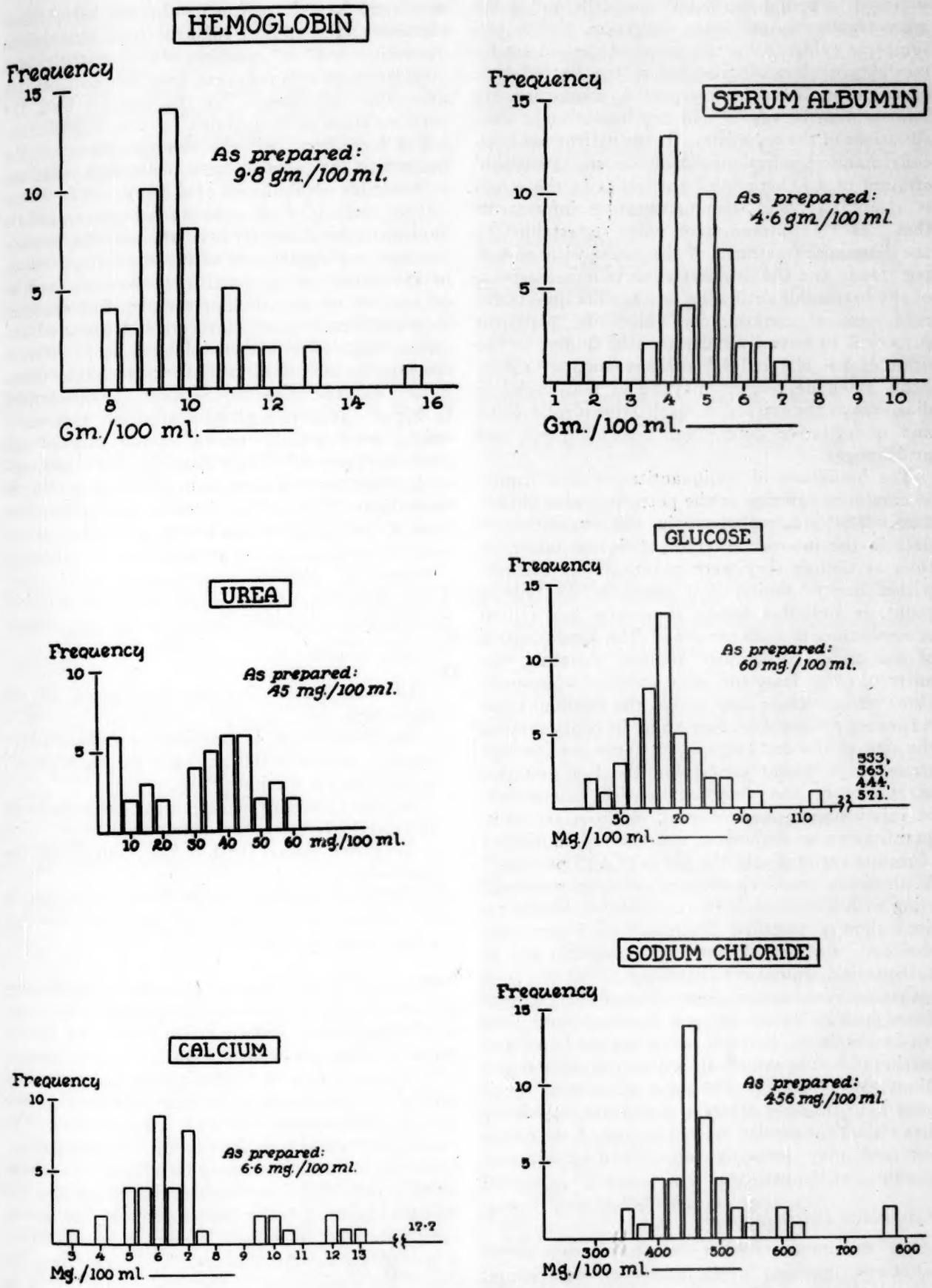

FIGURE 1. *Frequency Distribution of Results Obtained in Different Laboratories on Samples of the Same Known Solution.* (*Reproduced from Belk and Sunderman,[4] by Permission of the Publisher.*)
Half the published data are shown in the figure and are representative of the whole.

urine. If a spinal tap shows pus cells and a few gram-negative intracellular diplococci, this is presumptive evidence for treatment of the patient for meningococcal meningitis before the bacteriologic examinations have been reported, concerning the fermentation of sugars and the immunologic classifications of the organism. If the patient has clinically manifest infectious mononucleosis, the demonstration of 4+ heterophil antibodies in the serum is qualitative and semiquantitative information that has high presumptive value in establishing the diagnosis; treatment of the serum with guinea-pig kidney and the demonstration of nonadsorption of the heterophil antibodies is a further qualitative refinement of confirmatory value. In a patient suspected to have liver disease, the finding in the urine of 4+ bile and 4+ color reaction with Ehrlich's aldehyde reagent may be as meaningful in diagnosis as the extraction, qualitative identification and quantitative determination of bilirubin and urobilinogen.

The *limitations* of semiquantitative data require as careful recognition as the potential value of such data. The greatest abuse in the evaluation of data is the interpretation of semiquantitative results as though they were quantitatively accurate within narrow limits. For example, the red-cell count, in unskilled hands, frequently has a limit of significance of ± 20 per cent.* The determination of the mean corpuscular volume, therefore, has an error of at least the same order of magnitude. However, clinicians may accept the reported mean corpuscular volume at face value in characterizing the size of the red cells. Also, there are frequent errors in judgment concerning the interpretation of results of the determination of hemoglobin. In this instance, many clinical methods are semiquantitative, as employed, and the reproducibility of results varies within the limits of ± 15 per cent.* A physician may report "clinical improvement," using such a method, if two consecutive determinations show a so-called "increase" of 5 per cent; obviously, such a "change" in hemoglobin has *no* quantitative significance whatsoever.

Certain examinations depend upon the *preservation* of such biologic substances as casts or urobilinogen in the urine, bacteria in culture mediums and fixation of biopsy material. Semiquantitative determinations made on poorly preserved biologic specimens have inherent errors of significant magnitude that vitiate the results, waste the time of the examiner and may seriously influence diagnosis and treatment of the patient.

Quantitative Determinations

The continual addition of quantitative determinations, having known limits of significance, is evidence of the increasing applications of the scientific method in medicine for establishment of diagnosis and treatment. In the field of biochemistry, the clinical *value* of such quantitative determinations is manifest — for example, the measurements of blood sugar, urea, uric acid, calcium and other substances. In the biologic field, the determination of hemoglobin by the photoelectric-cell colorimeter and the determination of the hematocrit have made possible results that are reproducible within limits of ± 5 per cent.†

The *limitations* of quantitative determinations in medicine result largely from a failure to appreciate the limits of significance of the particular method, in the hands of the particular examiner, and as determined on a particular sample. For example, Belk and Sunderman[4] sent carefully prepared duplicate samples of known solutions to 59 different laboratories in Pennsylvania for quantitative determinations. The range of the results is summarized in Fig. 1. It is immediately apparent that many results were grossly wrong, would mislead the physician in establishing a diagnosis and might seriously affect the treatment and, therefore, the life of the patient. Belk and Sunderman received opinions from 95 pathologists concerning the causes of unsatisfactory results; these are summarized in Table 5.

Sources of error in quantitative determinations. A list of sources of error in quantitative determinations in medicine would include at least the following:

Objective errors (beyond the control of the examiner).

Sampling: error in obtaining a representative sample and in stability, such as preservation, of the biologic specimen.

Method: errors of measurement, of instruments of assay (specificity, reproducibility).

Subjective errors (within the control of the examiner).

Technical mistakes: errors of technical nature as related to quantitative measurement and proper control of the method.

Definition of the limits of quantitative significance of data. From the above discussion, it is apparent that a qualitative determination may have significance in diagnosis within wide limits of variation of the data. The very observation that blood is present in vomitus is a *qualitative datum* that determines the *presence or absence* of a substance. The crude observation that the vomitus contains a large, moderate or small amount of blood is a *semiquantitative* datum that has value even though the absolute number of milligrams of hemoglobin in the sample can be given only within wide limits. In a quantitative determination, it is necessary to define the significance of the final result if it is to be interpreted properly. This is most readily done by one of several statistical methods. The physician

*Two coefficients of variation.

†Two coefficients of variation.

of the future will demand information on the limits of significance of the results before he evaluates data in relation to the patient.

Statistical Analysis of Certain Data Obtained from Laboratory Examinations of Blood

No attempt is made in this paper to consider statistical methods in general, which are adequately described elsewhere.[5-11] The discussion here is limited to certain examples of evaluating, by statistical methods, the determinations obtained by about 20 different observers, examining samples of a single specimen of venous blood and using the procedures listed below. Such an exercise can be used to demonstrate the limits of significance of data obtained by different methods and to show improvement in the accuracy of observations resulting from training. The data can then be entered for analysis on a blank form, a portion of which is shown in Table 6. The results shown are typical data obtained by students in training who have already developed considerable proficiency.

Red-cell count. The red-cell count is performed in two ways. In the first of these two red-cell pipettes are filled, each being used to fill one counting chamber of a hemacytometer, 400 to 600 cells being counted in each chamber. The results of counts in the two chambers are averaged. Secondly, one red-cell pipette is filled and used to fill both counting chambers of a hemacytometer, the rest of the procedure being carried out as above.

Determination of hemoglobin. Five methods are used: the photoelectric-cell colorimeter (Evelyn), Spencer hemoglobinometer (American Optical Company), Sahli, Haden–Hauser and Tallqvist.

Hematocrit. The Wintrobe method is used.

Numerical Expression of the Degree of Deviation of Data; Calculation of the Standard Deviation

It is more convenient to express numerically, rather than graphically, the degree of variation of data, expressing the results as the standard deviation, S.D., or σ (small sigma). The standard deviation is calculated as follows, using the expressions commonly employed in statistical methods.

The arithmetic average, or mean, M is calculated by obtaining the sum Σ (capital sigma) of the total number N of observations, each observation being designated by the letter X. Thus,

$$\text{Arithmetic Average or Mean, } M = \frac{\Sigma X}{N}.$$

The deviation d of each observation from the mean is calculated by subtraction of the mean from it; $d = X - M$; d may be either positive or negative. The deviation of each observed value is then squared, to give d^2, and the sum Σd^2 of all the squares is obtained. The mean of the sum of the squares of the deviations $\Sigma d^2/N$ is employed in the finding of σ when N is large, but when the number of observations is small, as in the examples used here, the sum of the squares of the deviation is better divided by N-1 (see Fisher[7]). The standard deviation is calculated by determination of the square root of $\Sigma d^2/(N-1)$ — that is,

$$\sigma = \sqrt{\Sigma d^2/(N-1)}.$$

An example of the calculation from data for eleven red-cell counts is shown in Table 7.

Interpretation. Many biologic measurements tend to follow the so-called *normal distribution*, in which 95 per cent of the observed values fall within the

TABLE 5. *Factors Contributing to Technical Inaccuracies and Other Unsatisfactory Conditions in Clinical Laboratories.**

FACTOR	NO. OF TIMES LISTED
Poorly trained technicians	82
Inadequate number of technicians	80
Lack of understanding between pathologist and staff	64
Poor equipment	63
Insufficient floor space	57
Miscellaneous factors (inadequate orderly service, insufficient secretarial service and so forth)	39

*Based on data of Belk and Sunderman.[4]

TABLE 6. *Results Obtained by Different Medical Students after Considerable Training in the Examination of Samples of the Same Blood Specimen from a Patient with Cooley's Anemia.**

DETERMINATION	NUMBER OF OBSERVATIONS	MAXIMUM	MINIMUM	MEAN (AVERAGE)	TWO STANDARD DEVIATIONS (2 SIGMA)†	TWO COEFFICIENTS OF VARIATION %
Hematocrit (percentage)	10	25.0	23.5	24.1	±0.84	± 3.4
Hemoglobin (gm/100 ml):						
Photoelectric-cell colorimeter (Evelyn)	9	8.3	7.8	8.0	±0.36	± 4.5
Spencer hemoglobinometer	17	9.1	8.0	8.7	±0.78	± 9.0
Sahli	17	9.7	7.3	8.9	± 1.2	±14.0
Haden–Hauser	17	8.7	7.5	8.2	± 0.8	±10.0
Tallqvist	17	9.4	6.5	7.8	± 1.6	±21.0
Counts of formed elements of blood:						
R. B. C. (10^6/mm^3)						
(2 pipettes, 2 chambers)	20	2.5	2.0	2.2	±0.36	±16.0
(1 pipette, 2 chambers)	18	2.4	1.7	2.1	±0.28	±13.0
W. B. C. (10^3/mm^3)	18	11.6	7.55	9.1	±1.83	±20.0
Reticulocytes, wet method (per cent)	19	6.2	2.2	4.0		

*The limits of significance (two coefficients of variations) are representative of the methods themselves and indicate what may be obtained from any laboratory. The small error of the hematocrit and the hemoglobin determined by the photo-electric-cell colorimeter (Evelyn) should be especially noted.

†Units are those of the observations.

numerical limits M± 2σ — that is, between two standard deviations above and below the mean. The chance that a single observation will fall within these limits is therefore 95 in 100; the chance that it will fall outside these limits is 5 in 100. An observation falling outside these limits is thus considered abnormal, although the chance is 0.05 that it is not.

Numerical Expression of the Degree of Variation of Data; Calculation of the Coefficient of Variation

As the definition of σ shows, the limits of variation are always expressed in the same units as the quantity measured; thus, for the red-cell count, the units are millions per cubic millimeter, for hemoglobin, grams per 100 ml, and for the hematocrit, per cent. The standard deviations of determinations of red-cell count, hemoglobin and hematocrit cannot be directly compared with one another because the units differ. However, comparison can be made between quantities that have no units. For this purpose there is the *coefficient of variation*, C.V., which is defined as the ratio of the standard deviation to the mean, and may be expressed in per cent. Thus, C.V. $=(\sigma/M) \times 100$ per cent.

TABLE 7. *Example of the Calculation of the Standard Deviation σ from Eleven Determinations of the Red-Cell Count.*

Red-cell Count, X	Deviation from Mean d [=(X-M)]	d^2
millions/mm³	*millions/mm³*	
3.6	+0.1	0.01
3.7	+0.2	0.04
3.2	−0.3	0.09
3.5	0.0	0.00
3.6	+0.1	0.01
3.2	−0.3	0.09
3.5	0.0	0.00
3.4	−0.1	0.01
3.6	+0.1	0.01
3.5	0.0	0.00
3.5	0.0	0.00
$\Sigma X = 38.3$		$\Sigma d^2 = 0.26$

$$N = 11$$

$$M = \frac{\Sigma X}{N} = \frac{38.3}{11} = 3.5$$

$$\sigma = \sqrt{\frac{\Sigma d^2}{N-1}} = \sqrt{\frac{0.26}{10}} = \sqrt{0.026} = \pm 0.16 \text{ million/mm}^3$$

From the example in Table 7, where $\sigma = \pm$ 0.16 million red cells/mm³, it is found that

$$\text{C.V.} = \frac{\pm 0.16}{3.5} \times 100 = \pm 4.6 \text{ per cent}$$

The interpretation of two coefficients of variation (2 C.V.) is the same as that of two standard deviations (2σ), the only difference being the units of expression.

Summary and Recommendations

The physician himself will recognize the limits of significance of qualitative and semiquantitative determinations. However, he may have no way of knowing and, therefore, *must be informed* of the limits of significance of data obtained by a quantitative determination. Thus, it might be within practical possibility to record clinical data with a statement of the limits of significance, as indicated for certain tests in Table 6; for example, calcium, 10 mg/100 ml (2 C.V.± 5 per cent); red-cell count, 1.8 10^6/mm³ (2 C.V.± 14 per cent); hemoglobin 12 gm/100 ml (2 C.V.± 15 per cent); total protein, 6.2 gm/100 ml serum (2 C.V. ± 10 per cent). An individual laboratory worker can control subjective errors, and can determine and state precisely the objective error of any given method, with much benefit to the accuracy and significance of expensive and important laboratory results.

I am indebted to Mr. Joseph D. Elder, of the Harvard University Press, for contributions on the units of measure, and to Miss Jane Worcester, of the Harvard School of Public Health, and to Dr. Fred H. Allen, of the Children's Hospital, for aiding in the section on quantitative evaluation of data.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

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CASE 35391

PRESENTATION OF CASE

A forty-two-year-old handy man was admitted to the hospital because of anorexia and diarrhea.

The patient had been well until eleven years before entry, when he noted progressive enlargement of the lymph nodes of the neck. He was admitted to another hospital where a biopsy of one of the lymph nodes was performed and a subsequent diagnosis of Hodgkin's lymphoma rendered. He received several courses of x-ray therapy for recurrent masses in the neck with good results and was well until two years before the present admission when he was admitted to this hospital because of anorexia, vomiting, nausea and weight loss of 36 pounds of five months' duration.

Physical examination revealed a generalized superficial lymphadenopathy and a moderately enlarged spleen. A repeat biopsy of the axillary lymph nodes confirmed the previous diagnosis of Hodgkin's lymphoma. The patient was considered a "terminal problem" and was given six doses of nitrogen mustard following which he made a striking recovery, became asymptomatic, regained his normal weight and was soon back at work. Eight months later, however, because of recurrent symptoms and weight loss, he was readmitted and given five doses of nitrogen mustard following which he again responded dramatically with subsequent return to work. Four months before the present admission he was seen in the Tumor Clinic, where he complained of another recurrence of symptoms and at which time palpable inguinal lymph nodes were found. The patient was given x-ray therapy with diminution in the size of the masses in these areas. Six weeks before admission he returned to the Tumor Clinic, still complaining of nausea, weakness and weight loss. At this time physical examination failed to show any lymphadenopathy. One week prior to entry he complained of diarrhea of one month's duration. Stools occurred six to nine times daily, were watery brown without mucus or blood and were accompanied by severe cramps and tenesmus. There had been a 20-pound weight loss but no vomiting and only slight nausea. General malaise and weakness had been progressive.

Examination showed an emaciated, somewhat pale middle-aged man in no acute distress. There was slight to moderate generalized lymphadenopathy. The heart was not enlarged; the rhythm was regular, and the aortic second sound was greater than the pulmonic. A Grade I systolic murmur was present at the apex. The abdomen was normal except for considerable voluntary spasm. There was ++ pitting edema of the ankles.

The blood pressure was 100 systolic, 65 diastolic. The temperature, pulse and respirations were normal.

The urine was yellowish brown and gave a ++++ test for albumin. The sediment contained rare red cells and 5 to 10 white cells per high-power field and many granular casts. Examination of the blood disclosed a red-cell count of 3,300,000, with a hemoglobin of 13.3 gm., and a white-cell count of 11,100, with 89 per cent neutrophils. A smear showed a normocytic, normochromic anemia. A stool was guaiac negative.

Because of the patient's previous good response to nitrogen mustard therapy it was decided to treat him again in this way, and he was subsequently given five doses of 6.5 mg. of nitrogen mustard intravenously over a five-day period. After two days in the hospital, apparently in response to antispasmodic treatment, diarrhea decreased to one or two watery movements a day. The appetite remained poor, however, and symptomatically there was little change. A roentgenogram of the chest showed clear lung fields and no definite hilar-lymph-node enlargement. A barium enema was negative. Agglutination tests for brucella and organisms of the typhoid-para-typhoid group were negative.

On the fifth hospital day some presacral edema was noted, and there was a suggestion of a small amount of ascites.

On the sixth hospital day laboratory examination showed a serum protein of 3.54 gm. per 100 cc., with an albumin of 1.79 gm., and a globulin of 1.75 gm. per 100 cc. (albumin-globulin ratio of 1). The nonprotein nitrogen was 62 mg. per 100 cc., the sodium 126.5 milliequiv. per liter, the carbon dioxide 28 milliequiv. per liter, the prothrombin time 29 (normal 15 seconds), calcium 5.3 mg. per 100 cc., phosphorus 7.3 mg. per 100 cc., and phosphatase 6.1 units per 100 cc. A Congo-red test showed a small amount of dye in the five-minute specimen and almost none in the sixty-minute specimen. On the same day, during an attempted gastrointestinal series, the patient became very weak and upon return to the ward was found to be in shock, with a blood pressure of 60 systolic, 0

diastolic. The pulse was 120. Physical examination at this time did not reveal a cause for the change in the patient's condition, but peristalsis was noted to be absent. A roentgenogram of the abdomen was negative for free air. Following a transfusion of 1000 cc. of blood the blood pressure rose to 98 systolic, 58 diastolic. Despite this improvement the patient was still irrational at times. The skin was warm and moist, the lungs clear, and the heart rate 98 and regular. The abdomen was moderately distended, soft and diffusely tender but without rebound tenderness. Peristalsis was absent. There was no vomiting. On the seventh hospital day the patient appeared toxic but was not in the profound shock of the previous day. Early in the day the physical findings were unchanged, but later peristalsis was heard. A stool gave a ++ guaiac reaction, and the blood hemoglobin was 11.5 gm. Five hundred cubic centimeters of brown, watery fluid was aspirated from the stomach and gave a + guaiac reaction. Despite additional blood and supportive therapy the patient's course was progressively downhill. On the eighth hospital day he was incontinent and passed foul, yellowish-gray fluid material by rectum. Oral fluid intake was limited because of nausea, and intravenous fluid intake was intentionally kept somewhat low in the face of the ankle edema and ascites. The systolic blood pressure was 166. The nonprotein nitrogen remained low, and urine output was depressed. On the ninth hospital day he was found dead in bed.

Whereas urine examinations previous to this admission had been negative, six different examinations during this period of hospitalization gave ++++ tests for albumin, and the sediment contained 4 to 6 white cells and red cells per high-power field. All specimens contained numerous hyaline and granular casts. The specific gravity ranged from 1.012 to 1.015. The white-cell count, which had been 11,100 on admission, fell progressively to a low of 2200 on the seventh hospital day.

Differential Diagnosis

Dr. Charles L. Short: The original diagnosis of Hodgkin's disease in this patient was made by biopsy eleven years before his final admission. He had an unusually long remission, nine years, following the first course of x-ray therapy. It would be of interest to learn from the pathologist whether the original biopsy showed a less malignant type, according to Jackson and Parker's[1] classification, than the second one taken two years before his death. The patient was next treated with nitrogen mustard and twice made striking responses, with remissions lasting eight and ten months respectively. This case demonstrates the value, at times, of nitrogen mustard treatment.

Six weeks before his final admission, a new train of symptoms appeared that seemed to be localized to the gastrointestinal tract in the form of intractable diarrhea. The finding of generalized adenopathy on admission points to a recurrence of Hodgkin's disease, but the urinary findings can hardly be explained on that basis. The patient's course was rapidly downhill, with the development of edema and ascites and finally uremia. The episode on the sixth hospital day suggests intestinal perforation, with peritonitis, probably localized, or the point of perforation sealed off fairly rapidly, since peristalsis reappeared and there were never any frank signs of generalized peritonitis. The final discharge of foul fluid from the rectum may have represented perforation and drainage of an abscess by this route.

The next question to be decided is whether the patient died of Hodgkin's disease or a complication of this condition, or whether the treatment employed had anything to do with it. Perhaps a combination of these three factors was active. I think the diagnosis of amyloidosis secondary to Hodgkin's disease can be made with reasonable certainty in this patient in view of the nearly complete disappearance of Congo red from the blood stream. A recent paper from the Mayo Clinic[2] states that in 2 cases out of 30 of secondary amyloidosis the primary lesion was Hodgkin's disease.

The blood chemical findings revealed an elevated nonprotein nitrogen, a low serum protein and altered serum calcium and phosphorus values. I do not believe it is necessary to bring in the possibility of parathyroid destruction by amyloid or tumor to explain these calcium and phosphorus values. In fact, I do not know of any such cases as yet reported. Low serum sodium and hypotension suggest Addison's disease, which rarely occurs secondary to amyloidosis or to neoplasm. I think there is no way of making the diagnosis without further evidence, although amyloid deposits were probably found in the adrenal cortex at autopsy. This is a common site for secondary amyloidosis. Deposits were also probably found in the liver but not to the extent of producing any severe dysfunction of this organ. The increased prothrombin time may be accounted for by malabsorption due to the intestinal disease.

We are left with the diarrhea and probable intestinal perforation to explain. Although the small intestine may be involved in amyloidosis to the extent of diarrhea and even a sprue-like syndrome, I have been unable to find any cases going on to actual perforation. Nitrogen mustard in at least 2 cases[3] has apparently produced ulceration and perforation of the gastrointestinal tract, but this complication must be rare. Furthermore, this patient's diarrhea had started before the last administration of the nitrogen mustard. Involvement of the intestine is not uncommon in Hodgkin's disease and may lead to ulceration and perforation. I would prefer this explanation for the abdominal findings, with the possibility that the perforation was due to destruction of Hodgkin's tissue by the nitrogen mustard.

In summary, I believe the patient had Hodgkin's disease that involved the intestine, with perforation and peritonitis, and that he had secondary amyloidosis with the chief clinical manifestation of amyloid nephritis with uremia.

DR. JAMES B. TOWNSEND: He had some x-ray treatment toward the end in the inguinal region. Did he have enough to produce x-ray proctitis?

DR. SHORT: That is possible. I assume that he did not have large doses.

DR. STANLEY M. WYMAN: I do not know about that. Would you care to see the films, Dr. Short?

DR. SHORT: They were considered normal in the protocol. That is why I did not ask for them.

DR. WYMAN: I think there is some information that helps. The chest films were taken over a two-year period and show no significant intrinsic disease that I can recognize. The patient had a gastrointestinal series when first seen, and there is no evidence of definite intrinsic disease. The barium enema done on the last admission is not remarkable except for a poor demonstration of the cecum, which may be due to spasm at the time the films were taken. However, I cannot exclude organic disease in that region from these films alone. The films taken from the gastrointestinal examination done on this admission are quite striking. The first film shows a dilated, apparently fluid-filled stomach and a very markedly dilated duodenal loop. The second film, taken two hours later, shows no apparent progress of the barium from its original location in the duodenum. At that time several loops of dilated small bowel are seen scattered throughout the abdomen. A film taken two days after the gastrointestinal examination shows a very abnormal series of small-bowel loops, which are considerably dilated and still filled with barium from the gastrointestinal series taken two days before apparently. There is no gas in the colon, and none in the rectum. The x-ray picture represents an obstructive lesion in the lower ileum. I do not know how to tie it up with the picture in the cecum.

DR. BENJAMIN CASTLEMAN: What was the date?

DR. WYMAN: Two days before death.

DR. SHORT: That would be evidence for the possibility of tumor obstructing in that area.

DR. WYMAN: Mechanical obstruction in the loop of ileum or probably a paralytic ileus could look essentially the same.

DR. SHORT: Do you think the absence of air rules out the possibility of perforation?

DR. WYMAN: I think it is serious evidence against it, but I am not able to recognize a true film of the abdomen, taken in the upright position, to exclude that.

CLINICAL DIAGNOSES

Hodgkin's disease.
Uremia.
Amyloidosis?

DR. SHORT'S DIAGNOSES

Hodgkin's disease, involving intestine, with perforation and peritonitis.
Secondary amyloidosis, chiefly involving kidneys.

ANATOMICAL DIAGNOSES

Malignant lymphoma, Hodgkin's type, involving lymph nodes only.
Amyloidosis of liver, adrenal glands and especially of kidneys and lymph nodes.
Amyloid nephrosis (with uremia).
Acute enteritis.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: A review of the biopsy of the lymph node removed two years previously showed Hodgkin's disease, of the type that has been described by Jackson and Parker[4] as very early — what they call Hodgkin's paragranuloma. In this type the architecture of the nodes is not too markedly distorted; there is no evidence of fibrosis and only a few eosinophils, but the Reed–Sternberg cells are present. This microscopical picture would fit in with the long history of Hodgkin's disease that this patient had — thirteen years. Jackson and Parker[1] have reported cases in which patients with nodes of this character have lived for as long as twenty-five years and in which the nodes retain their paragranuloma appearance without ever going over into a true Hodgkin's granuloma or the more classic Hodgkin's disease.

Autopsy showed large numbers of nodes in the mediastinum and retroperitoneal areas predominantly, as well as in the cervical and axillary regions. Some of them were quite large, especially in the abdomen, along the aorta, forming masses reaching 9 cm. in length. When these were cut, they were quite firm and almost fibrous. Grossly it was believed to be Hodgkin's disease. Microscopical examination, however, showed that it was practically all amyloid. One has to hunt to find any cell that could be called a Reed–Sternberg cell of Hodgkin's disease. We sectioned about 20 nodes, and all showed the same picture: diffuse replacement by amyloid, with a periphery of cells and an occasional Sternberg cell. Going back to the original node removed two years before the final admission, we found no evidence of amyloid, so that we have evidence, I believe, that the amyloid developed within a two-year period. Since every node examined at autopsy was involved with amyloid, it would be a little farfetched to think that this particular biopsied node escaped at that time. We found no evidence of Hodgkin's disease in the liver, spleen, kidney or intestines. There was amyloid disease in the liver, kidney, and adrenal glands, but in no other organ, except the nodes.

The kidneys were very big, weighing 800 gm. together, which is about two and a half times the

normal weight, and they were very pale and glassy. There was very little evidence of scarring. Practically every glomerulus was involved with amyloid, but rarely was a whole corpuscle completely replaced. The striking finding in this case was in the tubules, which were plugged with casts, and the epithelial cells were swollen and filled with hyaline granules — characteristic of so-called amyloid nephrosis. The intestines, both colon and small bowel, showed scattered areas of hemorrhage, and on microscopical examination there was some cellular infiltration of the submucosa, an acute or subacute process, similar to what we have seen occasionally in uremia. There were, however, no ulcerations in the bowel. Whether this was due to the uremia or uremia in addition to the effect of nitrogen mustard, I do not know. I cannot account for the intestinal obstruction satisfactorily unless it was paralytic ileus as a result of uremia.

DR. WYMAN: I was thinking in terms of ileus as a result of vascular accident or uremia possibly to account for the picture.

DR. CASTLEMAN: The association of amyloidosis with Hodgkin's disease is not very common. Dr. Morgan, of our resident staff, looked up our cases and found that of 60 cases of Hodgkin's disease 5 had amyloidosis. It is interesting that in the series at the Boston City Hospital, reported by Jackson and Parker,[1] there was 1 case very similar to this one in which the amyloid was limited to lymph nodes, replacing them almost completely.

DR. JAMES H. CURRENS: Ileus has been described with potassium deficiency.[5] We have no information here, but it would be interesting to know whether he was losing excess potassium or retaining potassium. Occasionally, these patients, particularly with vomiting, can lose tremendous amounts of potassium, which may result in ileus.

DR. CASTLEMAN: What about the level of potassium in uremia?

DR. CURRENS: It may be high or low; it is usually high, but occasionally it may be low. Recently, a patient died in this hospital with a nonprotein nitrogen of 1.50 mg. per 100 cc., and a serum potassium of 1.2 milliequiv. per liter (normal, 3.5 to 5.0 milliequiv. per liter). It is a possible explanation.

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CASE 35392

PRESENTATION OF CASE

First admission. A thirty-nine-year-old housewife entered the hospital complaining of swollen legs.

At the age of fourteen the patient had severe pains in the feet and ankles. A heart murmur was noted, and she was kept in bed for about six months. With clearing of the joint pains she was allowed to resume normal activities but on doing so developed "Saint Vitus dance," described as purposeless twitchings of the hands and arms, which lasted about one and a half years, and then disappeared completely. The patient was well until the age of twenty-four, when, two weeks before the birth of her first child, she developed ankle edema that cleared spontaneously after delivery. She was then free of symptoms until one year prior to admission, when she developed palpitations and exertional dyspnea. Shortly before entry she noted ankle swelling, severe exertional dyspnea and orthopnea requiring three pillows, with almost weekly attacks of paroxysmal nocturnal dyspnea. There was no cough, chest pain, or fever.

Physical examination revealed marked engorgement and pulsation of the neck veins. Many moist rales were present throughout both lung fields. The heart rate was rapid and irregular, with an apical rate of 110 and a radial pulse of 96. There were enlargement of the heart to percussion and an apical systolic thrill. Harsh apical systolic and diastolic murmurs and a blowing diastolic murmur in the aortic area were heard. The liver edge was 5 cm. below the costal margin. The ankles and calves showed marked pitting edema.

The temperature was 99.2°F., and the respirations were 24. The blood pressure was 174 systolic, 98 diastolic.

Laboratory studies on the urine showed a specific gravity of 1.018, with a trace of albumin. Blood studies, including the white-cell count, nonprotein nitrogen, carbon dioxide and total protein, were not remarkable. An electrocardiogram demonstrated auricular fibrillation alternating with idioventricular rhythm. X-ray studies of the chest showed a small amount of fluid in the left costophrenic angle and considerable generalized cardiac enlargement.

Following digitalization the patient improved steadily until two and a half weeks had elapsed, and then she suddenly developed severe pain in the right lower chest and hemoptysis. Roentgenograms revealed a large area and several smaller areas of increased density in the right lower lobe. Surgical interruption of both common femoral veins was done, but no clots were found. Improvement was slow but steady, and after three months the patient returned home on a regimen of digitalis, ammonium chloride and weekly injections of mercuhydrin.

Second admission (four months later). The patient did well until approximately four months

after the first admission, when she again developed severe pain in the lower chest for which she was readmitted. Chest x-ray films showed a new area of increased density in the anterior portion of the right lower lobe. Heparin and dicumarol were instituted, and shortly thereafter she became asymptomatic and was discharged two weeks later.

Final admission (one year later). Over the ensuing year the patient enjoyed limited activity and was fairly well until two weeks prior to re-entry. Rather suddenly she became extremely nervous and jittery and developed coarse, involuntary tremor of the hands and feet. She had several, apparently unprovoked, episodes of uncontrollable shrieking and crying and other sudden episodes of confusion, disorientation and memory disturbances. With the onset of these symptoms she noted a diffuse, slightly itchy erythema of the hands, feet and extensor surfaces of the forearms and lower legs. There was no fever, chills, chest pain or hemoptysis, and no evidence of embolic phenomena.

On physical examination the patient lay in bed in no acute discomfort, but there were occasional twitchings of the hands and feet. There was a diffuse, rose-red erythema over the dorsal surfaces of the hands and feet and the extensor surfaces of the legs and forearms, which blanched on pressure. The skin was cool and moist. The neck veins were engorged and pulsating. The lungs were clear except for an area of dullness at the right posterior base. The heart showed no change from previous examinations. The remainder of the examination, including the neurologic examination, was negative except for moderate pitting edema of the ankles.

The temperature was 97°F., the pulse 88, and the respirations 20. The blood pressure was 130 systolic, 90 diastolic.

Examination of the blood revealed a white-cell count of 12,000, with 66 per cent neutrophils, 25 per cent lymphocytes, 6 per cent monocytes, 2 per cent eosinophils and 1 per cent basophils. An electrocardiogram showed a rate of 90. The QRS complex was 0.07, and the T waves were obscured by coarse auricular fibrillations. There was right-axis deviation. Chest x-ray films showed linear scarring in the region of the previous densities in the lung fields and little change in the heart. The sodium was 139.5 milliequiv., and the chloride 102 milliequiv. per liter and the nonprotein nitrogen 66 mg. per 100 cc.

The erythema had disappeared, and the coarse tremors of the extremities had diminished by the day after admission. Over the next two days, however, the patient's behavior became more bizarre, with almost continuous hysterical crying and thrashing about the bed. Much of the time she seemed entirely out of contact with her surroundings. Despite the marked behavior change, examination showed only cyanosis of the extremities and a dusky, reddish-purple discoloration of the skin. Her condition rapidly deteriorated, and by the sixth hospital day she was completely unresponsive. The cyanosis had gradually deepened, and she became markedly dyspneic and hyperpneic. The apical pulse was 112, and the radial pulse 52. However, the lungs remained clear. Despite oxygen therapy the cyanosis progressively deepened, and the pulse gradually weakened. The temperature spiked to 105°F., the circulation slowly failed, and she died on the seventh hospital day.

Differential Diagnosis

Dr. Gordon S. Myer: This patient seemed to present no unusual problem until the time of her third and final admission to the hospital. There is a history perfectly consistent with the occurrence of active rheumatic fever and chorea at the age of fourteen, at which time a heart murmur was noted. The onset of rheumatic fever as late in childhood as this and the associated chorea would both favor a relatively good prognosis. This was borne out since she was apparently quite well until the age of thirty-six or thirty-seven years except for one brief episode of ankle edema, which may or may not have represented mild congestive failure toward the end of her pregnancy at twenty-four years of age.

One year prior to her first admission to the hospital the patient went into definite congestive heart failure associated with palpitation, which evidently represented the onset of auricular fibrillation. Such an association between the occurrence of auricular fibrillation and the appearance of heart failure is certainly common in patients with rheumatic heart disease. Physical examination indicated the presence of pulmonary congestion and right-sided failure on the basis of rheumatic heart disease with mitral stenosis and regurgitation and aortic regurgitation and auricular fibrillation and with a rather rapid ventricular rate and a pulse deficit. In addition, a slight hypertension was present and there was some albuminuria. The appearance of a small amount of fluid in the left pleural cavity makes one think of pulmonary embolus even then, since in uncomplicated heart failure the right pleural cavity is most apt to accumulate fluid first. In any case, she later evidenced the classic signs and symptoms of pulmonary emboli, for which femoral-vein ligation was carried out. She was then sent out on routine therapy for control of the congestive failure.

The second admission to the hospital was occasioned by the recurrence of chest pain. When chest x-ray films revealed changes consistent with a new pulmonary infarct she was given anticoagulant therapy. Where did the embolus arise? It may, of course, have come from the common femoral arteries above the point of their ligation or from veins in the pelvis, but a more likely source would be a thrombus in the right auricle.

We now come to what I believe is the central problem. What was the nature of the complication

that led to the patient's death? Since the onset of her terminal illness was characterized by tremors and disorientation and the appearance of a pruritic dermatitis, one immediately wonders about medication. May we know what drugs she had been receiving between the second and third admissions? Had she been taking lithium chloride as a salt substitute?

DR. BENJAMIN CASTLEMAN: She had been followed in the Out-Patient Department and given digitalis, ammonium chloride and mercurial injections. In addition she had been put on a low-sodium diet and had been given a lithium chloride preparation starting about a month before her final admission to the hospital.

DR. MYERS: Do we know how much lithium chloride the patient actually consumed? Also, did she continue to receive the salt substitute after admission?

DR. CASTLEMAN: There is no record of the actual amount ingested. She did continue to receive the salt substitute ad lib. after admission to the hospital.

DR. MYERS: It would be possible to explain this patient's coarse tremors and disorientation on the basis of lithium intoxication. She apparently was taking it for only a short time prior to the onset of her acute symptoms, but she may have taken far more than was recommended, as some patients do. Also we learn that her renal status was unsatisfactory, with a nonprotein nitrogen of 66 mg. per 100 cc., so that the excretion of lithium may have been unusually poor. As far as I know lithium poisoning has not been associated with the appearance of a skin rash, however. Neurologic manifestations of digitalis toxicity, including restlessness, disorientation, delirium and tremors, in the absence of other evidence of digitalis poisoning have been reported, but these are certainly very rare and again would not account for the pruritic erythema of the skin. She had apparently not ingested bromides, barbiturates or salicylates. It seems highly unlikely that the mercurial injections can be implicated. Patients on the low-sodium diet may occasionally become weak, confused or comatose, with a high nonprotein nitrogen and low serum sodium level, but that was not the picture here. Although mental aberrations on the basis of cortical-vessel involvement in rheumatic fever have been considered to occur, the evidence for this is unsatisfactory, and the associated erythema as described is not like that of the rheumatic erythemas ordinarily encountered. The neurologic examination was negative, and the evidence does not favor the occurrence of multiple cerebral emboli from the left auricle or from a focus of bacterial endocarditis on the mitral or aortic valves. I am forced to the conclusion that this patient had a "toxic" psychosis in association with congestive heart failure, cerebral anoxia and azotemia. Lithium intoxication may also have played a role. I cannot satisfactorily explain the skin rash, and that is disturbing.

We are still left with the problem of the final cause of death.

At the time of her final admission the patient exhibited signs of right-sided cardiac failure without evident pulmonary congestion. The heart murmurs were unchanged, and the auricular fibrillation was moderately well controlled as to ventricular rate. There was no elevation of temperature or marked leukocytosis, and the chest x-ray film failed to reveal fresh pulmonary infarcts. The appearance of right-axis deviation in the electrocardiogram, not mentioned as having been present at the time of the first admission, may have been on the basis of mitral stenosis and due to right ventricular strain resulting from repeated pulmonary emboli as well. The elevated nonprotein nitrogen may merely represent prerenal azotemia on the basis of congestive heart failure. What did urinalysis show at the time of the last admission?

DR. CASTLEMAN: The specific gravity was 1.012, with a +++ test for albumin and the sediment showed 15 to 20 epithelial cells per high-power field and a few white cells but no red cells.

DR. MYERS: Heart failure could also account for the presence of albuminuria. We seem to have no evidence, other than the rather low specific gravity, to suggest complicating renal disease.

The last few days in the hospital were marked by a rapid downhill course, with delirium followed by coma. She became progressively more cyanotic and dyspneic; tachycardia became more marked, and a sharp temperature elevation occurred just before death. Despite marked respiratory distress the lungs were clear. I believe that terminal pulmonary embolism or thrombosis in the pulmonary arterial tree may explain this picture. In such a case actual new pulmonary infarcts may or may not have occurred. Active rheumatism cannot be ruled out.

In conclusion, I believe this patient had rheumatic heart disease, with mitral stenosis and regurgitation, aortic regurgitation and auricular fibrillation. Evidence of active rheumatic fever may have been found. Congestive heart failure was certainly present. In addition, I would postulate recurrent pulmonary emboli, perhaps arising from the right auricle, with terminal pulmonary embolization or thrombosis within the pulmonary arterial tree and cor pulmonale leading to death. I think the azotemia and albuminuria were more likely due to congestive failure than to complicating intrinsic renal disease. A "toxic" psychosis, with perhaps some element of lithium intoxication, seems the best explanation of the episodes of confusion and delirium so prominent at the time of her terminal illness.

Clinical Diagnoses

Rheumatic heart disease with mitral stenosis.
Auricular fibrillation.
Progressive cerebral thrombosis.

Dr. Myers's Diagnoses

Rheumatic heart disease, with mitral stenosis and regurgitation, aortic regurgitation and auricular fibrillation.
Active rheumatic fever?
Pulmonary embolism, from right-auricle thrombi, with cor pulmonale.
Toxic psychosis from lithium intoxication?

Anatomical Diagnoses

Pulmonary embolism, massive, acute.
Mural thrombi, both auricles.
Endocarditis: chronic active rheumatic, mitral and aortic, with mitral stenosis.
Healed pulmonary infarcts.
Congestion of lung, liver and spleen.
Cerebral emboli, microscopic.
Cardiac hypertrophy, right.
Renal infarct.

Pathological Discussion

Dr. Castleman: Post-mortem examination showed an enlarged heart, weighing 430 gm. There was marked dilatation of both auricles and dilatation and hypertrophy of the right ventricle, which was about twice normal in thickness — findings characteristic of the mitral heart. This was confirmed when the heart was opened, the mitral orifice barely admitting the tip of the little finger. Although the aortic cusps were thickened and in places calcified, there was no evidence of interadherence to produce any stenosis. Microscopically, above the margins of both valves there was active fibroblastic proliferation consistent with chronic active rheumatic infection. Although I could find no Aschoff nodules in the myocardium, I believe the cellular proliferation in the valves indicates a process that was still in a healing stage.

As evidence of the auricular fibrillation we found mural thrombi in both auricular appendages, and these probably were the source of the emboli to the lungs from the right auricle and to the kidney and brain from the left. There were both old and recent emboli within the pulmonary circuit, the recent ones being in the main vessels and the immediate cause of death; the older ones were in the smaller vessels and in relation to healed infarcts.

In several microscopical sections of the cerebrum, there were many small arteries occluded by old recanalized thrombi as well as more recent occlusions, unquestionably representing emboli. There were a few small foci of infarction. There was no evidence of an endarteritis, and I believe that many of the cases of so-called rheumatic endarteritis are probably on an embolic basis. There were no changes to suggest a toxic process.

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SIGNERS OF THE PROTEST

THE signers of the Protest of January 31, 1949, to the American Medical Association have continued since that time to lead a loosely corporate existence. Their original protest was against the levying of the famous twenty-five dollar assessment unless or until some adequate guarantee could be given that the policies and methods of the Association in combating compulsory health insurance would be more constructive and progressive than previous indications had led one to expect.

The same unhappy flair for infelicitous publicity that characterized the actions of the House of Delegates in adopting the assessment and, at a subsequent meeting, in repudiating the Association's editor greeted the protest. As a result a number of physicians who had only the welfare of their profession at heart came under the suspicion of having betrayed organized medicine instead of guarding its honor with more than ordinary zeal.

Since that time a number of the signers of the protest have paid the assessment — some, no doubt, because they acknowledged the legality of the levy, regardless of its purpose, others because of a reasonable assurance that the Association was really embarked on a constructive campaign for the equitable distribution of medical service. The announcement of a national representative health assembly to be held this fall gave promise also that the Association's twelve-point program, existing at present only as a statement of impeccable principles, might in reality become a program, devoted to action.

The signers of the protest have continued to interest themselves in health legislation, and have shown a commendable desire to keep informed on the subject. Most recent interest in this respect has had to do with the Flanders–Ives Bill (S. 1970) and its identical companion House bills (4918 through 4924), introduced by Messrs. Herter, Javits, Case, Nixon, Morton, Fulton and Hale. The opinion of the "signers" has been sought on this prospective legislation in the light of a statement made by Dr. George Baehr on behalf of the New York Academy of Medicine, at the public hearings before the Senate Committee on Education and Labor, on June 20, 1949.

The Academy, which, in 1946 and 1947, urged enactment of legislation "to provide federal grants-in-aid to the states for the study of state and local needs and the development of state and local programs designed to correct those deficiencies in accordance with acceptable federal standards," is not interested in maintaining the status quo. It is, on the contrary, "prepared to consider any change in the methods of rendering medical services and of payment for medical care which may be better for the people."

S. 1970, according to Dr. Baehr, comes most nearly, of all the bills under consideration, to meeting all the Academy's requirements for a voluntary prepaid comprehensive medical-service plan. Two excellent features of the bill are the provisions for the gradual development of its program, with the encouragement of medical groups,

and the creation of a bipartisan federal health study and planning commission to make a survey of health service needs and report to Congress in 1953.

The fears of the Subcommittee on National Legislation of the Massachusetts Medical Society, as expressed last May to Congressman Herter, are that this bill, if passed, would ultimately result in the absorption by the federal Government of voluntary, nonprofit, prepayment medical and hospital-care plans. No mention is made in it of employer contributions, nor is the method of financing clearly defined. Ostensibly subscribers would pay in accordance with their ability to pay, the chief financial burden being carried by those with greater-than-average incomes, who would pay in much more than they would take out.

What is obviously needed more than anything else, if the best health plan possible is to be devised for the nation, is a meeting of the most capable minds, without heat and without acrimony.

FOOD FOR THOUGHT

THE latest program undertaken by "CARE"—Cooperative for American Remittances to Europe, Inc.—is to provide food for the hungry intellects of Europe. Reduced indeed is the pabulum that nourishes the mind, for at no time in the history of the world have so many books been destroyed as in the past decade.

In Prague, as a result of the War, the Research Institute of Medical History of Charles University lost 16,000 of its 20,000 volumes. The Public Library of Corfu, Greece, lost 70,000 volumes. The University Library in Vienna lost 150,000, and the British Museum Library in London 250,000. The National and University Library of Strasbourg lost 300,000 of its prewar collection of 800,000 volumes, and 900,000 were destroyed at the University Library of Louvain, which had been devastated in 1914 and since rebuilt with American aid. The need for books, never satisfied, has become desperate.

CARE, having sent literally millions of food and textile packages overseas from Americans, now, in its "Food for the Mind" program, has its representatives in other countries, in co-operation with those of UNESCO, collecting lists of the books in certain specified fields needed by the universities, libraries and technical schools of fourteen nations. Only new books are being sent, and these, published in English, are selected from a list prepared by a committee headed by Dr. Luther Evans, librarian of Congress, and composed of thoroughly qualified scientists and librarians. The categories covered include health and welfare, medicine, dentistry, applied science, nursing, agricultural science, veterinary science and English-language instruction. Deliveries are being made to institutions only, in Austria, Belgium, Czechoslovakia, Finland, France, Greece, Italy, Japan, Korea, the Netherlands, Norway, Great Britain, the three western zones of Germany and all Berlin, and negotiations with Poland are pending.

Contributions of money in any amount will be received by the CARE Book Program, 20 Broad Street, New York City, or by any CARE office in the country. Donors of ten dollars or more may specify the institution and country to which books shall be sent, and the category in which the books may fall, but not the titles.

With many freedoms lost, there are still those left to which the knowledge gained from books can lead the way.

DIABETES WEEK, 1949

DIABETES Week this year will commence on October 10 and will constitute a particular "week" to which none need object. The purpose of its observance is an unusual, concentrated effort to find as many as possible of the million undiscovered diabetic persons in the country.

The most important specific function of this drive will be the performance of the simplest fundamental test for the discovery of diabetes — the examination of the urine for the presence of sugar of as many persons as can be persuaded to have the test performed. This testing will be done generously, freely, and by as many agencies and under as many auspices as may seem wise and practicable.

The important agent, however, must be the physician, who has available the necessary follow-up technic and who will find in this occasion an op-

portunity to demonstrate publicly that his real concern in the practice of medicine is that of service rather than reward. This is a lesson to be impressed upon a somewhat skeptical public that is inclined to find actions more eloquent than words.

PRIZE-ESSAY COMPETITION

THE *Journal* announces that a prize-essay contest will be open to all members of the class of 1950 registered in any medical school approved by the Council on Medical Education and Hospitals of the American Medical Association. The subject of the competition will be "Recent Advances in the Recognition, Treatment and Control of Poliomyelitis."

As in the previous competition, the purpose is to encourage good medical writing as well as to promote the collection of scientific material, and particular weight will therefore be given to such qualities as clarity, simplicity and general literary distinction. The conditions of the contest are unchanged: manuscripts should be between four and five thousand words in length, clearly typewritten in English, double or triple spaced, with references listed at the end in numerical sequence according to the form used by the *Quarterly Cumulative Index Medicus*. Papers must be in the hands of the editor by March 15, 1950. All manuscripts will become the property of the *Journal*.

The prize for the best essay among those submitted for consideration will be $100. The paper will again be published in the "Medical Progress" series, and the author will receive a hundred free reprints.

The second prize will again consist of a two-year subscription to the *Journal*.

The prize-winning essay for 1949, entitled "Preventive Medicine," by Dr. Miriam D. Manning, of the class of 1949 at Tufts College Medical School, appeared in the June 30 issue of the *Journal*. It is hoped that the essays for 1950 will come up to the high standard set by Dr. Manning's essay, which demonstrated the quality of medical writing that physicians should be capable of and which the judges unanimously awarded first prize.

By the influence of a pretended clairvoyant mesmerizing female over vulgar minds, an elaborate and patient examination of the manure of a large stable was recently made in Boston, to find the body of a missing expressman, whom she declared had been murdered, and was there concealed. On Monday, of last week, the defunct reappeared in the city, in excellent condition!

Boston M. & S. J., *September 26, 1849*

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

LANG — Walter E. Lang, M.D., of Westboro, died on September 11. He was in his sixty-seventh year.

Dr. Lang received his degree from Hahnemann Medical College and Hospital of Philadelphia in 1910. He was a member of the New England Society of Psychiatry and the American Psychiatric Association and a fellow of the American Medical Association.

His widow, a daughter and a son survive.

MANDELL — Augustus H. Mandell, M.D., of New Bedford, died on September 3. He was in his eighty-second year.

Dr. Mandell received degrees from New York University Medical College in 1897 and Cornell University Medical College in 1899. He was resident physician at Sassaquin Sanatorium in New Bedford.

His widow survives.

McFEE — William D. McFee, M.D., of Haverhill, died on September 7. He was in his seventy-fifth year.

Dr. McFee received his degree from University of Vermont College of Medicine in 1897. He was president of the American Academy of Physical Medicine and was a fellow of the American Medical Association.

His widow, four daughters and two sisters survive.

CORRESPONDENCE

STUDY OF TWINS

To the Editor: The study of twins is of great value in providing information concerning the respective importance of hereditary predisposition and environmental influences in disease in man. The results of the use of this method have shown a hereditary predisposition to tuberculosis, diabetes and tumor formation, and a high, medium or low intelligence quotient.

There is some *a priori* evidence of a hereditary predisposition for peptic ulcer. Only 6 cases of peptic ulcer in either or both of monozygous or dizygous twins have been reported in the readily accessible literature. Since twins are born in 1 of 86 births and identical twins in 1 of 344 births and the general incidence of ulcer is from 5 to 10 per cent, there should be plenty of material available.

I should like to ask physicians to co-operate in assembling such material by sending me information regarding cases in which one or both twins develop peptic ulcer, the site of the ulcer, the age of the patient at onset of the ulcer, the type of twins (monovular or diovular), the sex and date of birth of the twins and the number and age of the brothers and sisters and the absence or presence of ulcer in each.

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Department of Clinical Science
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DIFFICULTIES OF GENERAL PRACTICE

To the Editor: Having recently made the transition from one of the larger teaching hospitals to a rural general practice, I feel called upon to comment on your editorial of August 11 entitled "Education of the Family Physician."

As one of a bewildered group of young men who have recently finished medical school, I was faced with the problem of specialization. My environment and conditioning has been such that, seemingly, the man who was in general practice was a man who had unsuccessfully competed for some type of residency and so was ungracefully thrust out into the world to make a living with the unspecialized knowledge that he had managed to accumulate. I, too, had been guilty many times of referring patronizingly on hospital records, to the "L.M.D."

However, with the passage of time and the increasing size of my family, it soon became apparent that I should not be able to go on with my training — that soon I must earn a living. And medicine had reached the stage where it could be said that the "renaissance of the general practitioner" was upon us. There was the increasing agitation by the American Medical Association for more general practitioners, specialization had begun to be viewed with alarm, there had been created a General Practitioner of the Year Award, and a new group, the American Academy of General Practice, had made its appearance. It is in this favorable era that I have begun my general practice.

And after four months of rural general practice I believe that I can begin to make some comments on the status of my medical education. First and foremost, it is not advancing as it used to. The editorial referred to above glibly states that "The family doctor is likewise to blame by trying to do too much and becoming so busy he cannot keep up with attendance at meetings or with medical literature. Instead he would do well to put such educational activities on a required list each week." When one works seven days a week for twelve to fourteen hours and more a day, one finds it difficult to keep up with what is going on. My journals are only glanced through because I find myself too busy. Is it the patients' fault? I don't know. Perhaps in a while the novelty of "the new doctor" will wear off. But what I am getting at is: that, through apparently no fault of my own, I have become too busy and don't know what to do about it. One can hardly refuse to see patients in an area like this if they call one.

Secondly, educational opportunities for the rural practitioner, particularly in this area, are almost nil. There are no hospitals that contain ward beds for me to visit and observe. What shall I do? When one is located hundreds of miles from teaching centers, getting to them is more easily said than done, especially if one dare not leave because of critically ill patients who cannot be turned over to anyone during one's absence.

Finally, membership in the American Academy of General Practice, a purported stimulus to education, excludes the neophyte who is just beginning his practice. He must have completed three years of general practice before being considered for membership. This hardly leads to encouragement for a man to continue his education if he is excluded from the few educational opportunities that may be open to others but not to him, simply because he has not "put in enough time" to become a member. And, in three years, who knows whether the requirements for membership will have been made even more rigid and I, and men like me, will be unable to qualify for membership. Yesterday there was no American Board of Proctology.

What is the answer? Certainly, it cannot be that the general practitioner in an area like this is at fault. Perhaps it is society, or perhaps it is the physicians themselves who have banded together and made tight centers of learning, meccas toward which many of us aspire but for the nonce are unable to enjoy. There are many like myself, I am sure, who would like to be heard. There must be because my colleagues who are near me have the same problems. Are we to blame for our stagnation? Perhaps I am rationalizing when I say, "No."

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BOOK REVIEWS

Psychiatry: A short treatise. By William A. O'Connor, L.M.S.S.A. (Lond.), D.P.M. (Lond.). 8°, cloth, 380 pp. Baltimore: Williams and Wilkins Company, 1948. $9.00.

For an adequate review of this textbook one would need to know not necessarily the literature and history of the development of psychiatry as practiced in Great Britain, but rather the attitude and emotional reaction toward psychiatry and its therapeutic approach as manifested by the psychiatrists of today. The author states, both in the preface and in the body of the text, that his approach is that of psychosomatic medicine. The impression is gained, however, that here is a man torn between two worlds: the organic and the functional, or the descriptive and the dynamic analytical.

On the whole, the material is well organized. Too often, definition of terms and mechanisms are left to haphazard search on the part of the beginner. The chapter on "Symptoms of Mental Disease" and that on "Psychic Mechanisms" are a distinct step forward in the understanding of a new subject. To present the various paranoid reactions as a group is probably well justified and leads to clearer thinking, although one still must consider it a type of schizophrenia, as long as the official classification continues, and the author rightly does so. "Analytic Therapy and Theory" is also a logical introduction inasmuch as the author tends toward an eclectic approach. Other than the above, the general outline of each chapter devoted to each of the major groups of the psychoses (namely, "History," "Aetiology," "Psychopathology," "Symptomatology," "Diagnosis," "Prognosis" and "Treatment") is systematic and conducive to clear thinking.

Only a beginner can tell what a beginner gets out of an introductory text to psychiatry. Had there been no effort by the author to set forth a thesis, one would have little to remark about, either for originality or lack of it. As it is, there is the curious feeling that the past still influences too much, that description takes the place of dynamics, that psychiatry is still the handmaiden of neurology and that the functional is still overshadowed by the organic. Whether one or the other should prevail is entirely beside the point. One gets a little of the impression one does of "Lot's Wife." The author intellectually is walking into the future, but emotionally his face is turned to the past.

Conditioned Reflexes and Neuron Organization. By Jerzy Konorski. Translated from the Polish under the author's supervision by Stephen Garry. 8°, cloth, 267 pp., with 18 illustrations. Cambridge, University Press; New York, Macmillan Company, 1948. $4.00. (Cambridge Biological Studies.)

This book undertakes the task of "attempting to extend the Sherrington conception of the functioning of the nervous system to the field of higher nervous activity." An effort is made to close the gap between Sherrington and Pavlov in the field of neurophysiology. The accomplishment is particularly commendable because the work was made much more difficult by the loss of original manuscripts and research notes as a result of war damage to the Nencki Institute of Experimental Biology in Poland. The material is presented in a clear, concise style when allowances are made for the fact that this is a translation from the Polish language. The translator should be complimented for the precise way in which he has executed his task. This short book is provocative and encourages a more adequate approach to the problem of higher cerebral integration. It definitely is a landmark for further research in the field of neurophysiology.

The author finds no conflict with the neuronic theory of the functioning of the nervous system. The ideas developed in his research fall into the framework of this theory. However, the point is presented that the activity of the cerebral cortex is associated not only with the idea of excitability and the inhibition of transmission of impulses but also with new paths for these stimuli to travel on their complicated journey.

Three assumptions are made to account for these properties. The first is that "the elaboration of a condition reflex consists in the formation of new connexions in the brain, or rather that there can be the formation and multiplication of synapses between coupled cerebral centres." Secondly, it is postulated that if "a combination of excitations which results in a plastic change is not repeated within a certain period,"

the regression of this change may occur. Thirdly, "internal inhibition being a process that arises with non-reinforcement of the established condition reflex consists in the formation of new synaptic connexions of an inhibitory nature, independently of the already existing excitatory synaptic connexions." Although an attempt is made to correlate the physiology of the higher nervous activity with neurophysiology, the author well recognizes the limitations of his own presentation, several of which he mentions. He states that he is concerned in this book with "lowest levels of cortical coordination" and that he has come up against many facts that because of their complexity are not fully covered by the principles he attempts to lay down. He presents a challenge of trying to understand cortical and subcortical cerebral function in relation to human mental activity. He seems to believe that the physiology of the higher nervous activity is now at the stage that physics reached several centuries ago.

The format of the book is good, and a good index covers a rather general table of contents. The reader is able to become familiar with much of the Russian literature, which is difficult to translate. In spite of some of the verbosity that may be attributed somewhat to the difficult task of translation, this book is recommended for those who are interested in the complicated field of cerebral physiology.

Reproduction and Survival. By R. Christie Brown, M.B., M.S., F.R.C.S., F.R.C.O.G. 12°, cloth, 108 pp. London: Edward Arnold and Company, 1948. $2.25.

In this remarkable monograph, the author presents a well known British obstetrician's concept of the philosophy of reproduction as a means of racial survival, viewing embryology as a biologic phenomenon. Reproduction is a racial, not an individual, process whose objective is to guarantee survival of the species. In the contest for survival, in which the individual is merely a pawn in the game, various patterns of reproduction, adapted to the environment, have been employed. Civilization mitigates some of the stresses of nature in the struggle to live in a highly hazardous and competitive universe, and physical death is defeated by the rejuvenation of tissues at reproduction. But civilization introduces new hazards of its own, and medical science sometimes makes possible the temporary survival of the unfit and the perpetuation of undesirable qualities. Abundant reproduction, continuous variation and unhampered natural selection are the essentials of racial survival and evolutionary improvement amid the thrusts and parries of a dangerous world. To a certain limited extent parental care, co-operation and sacrifice may substitute for free reproduction, but declining human birth rates are the danger signals of progressive racial deterioration and decay. The only physical immortals are the species and the germ cells, the fateful race of zygotes. Man, who alone has developed an organism capable of harboring spirit, is more concerned with the individual than with the species, but nature is concerned only with the survival of living forms:

So careful of the type she seems,
So careless of the single life.

Dementia Praecox: The past decade's work and present status: A review and evaluation. By Leopold Bellak, M.D. With a foreword by Winfred Overholser, M.D. 8°, cloth, 456 pp., with 8 illustrations. New York: Grune and Stratton, 1948. $10.00.

As stated in the subtitle, Dr. Bellak presents in this work a review and evaluation of the work of the past decade concerning the problem of schizophrenia. He presents a well systematized and readable review of all the major investigative work that has been done in the past ten years, and correlates the numerous isolated facts from both the organic and the psychogenic standpoints concerning the etiology, psychogenesis and psychopathology of schizophrenia. In addition, he gives a well integrated evaluation of the various forms of therapy and technic.

This work presents in one volume the results of extensive research concerning this problem and therefore provides a valuable summary of present knowledge of schizophrenia. The volume should be of great value to those interested in this problem and of equal, if not greater, importance to those who are initiating their study of schizophrenia, presenting as it does a complete summary of existing knowledge and directing the reader's attention to future avenues of investigation.

Muscles: Testing and function. By Henry O. Kendall and Florence P. Kendall. 4°, cloth, 278 pp., with 162 illustrations. Baltimore: Williams and Wilkins Company, 1949. $7.5

This atlas on the testing and function of muscles is refreshingly clear and easy to read. The photographs of the contracting muscle on the subject are excellent and give a vivid picture of the movement performed. The muscles of the upper and lower extremities, the back, the abdomen and face are shown and described in turn. For completeness, one would have liked to see a fuller description of the muscles of the eye and the buccal cavity. But the testing and training of these muscles is probably outside the function of the physiatrist. There is a concise descriptive text accompanying each photograph. There are charts of the origin and insertion of the varying inner ration of muscles. The methods of recording muscular efficiency are carefully described. This work appears at an appropriate time when there is renewed interest and improved technics for the rehabilitation of the handicapped. Its careful arrangement and illustration should recommend it for the training and guidance of physicians and physiotherapy technicians as a valuable guide in assaying physical disabilities. The Kendalls are to be congratulated for producing so useful and pleasing a treatise.

Present Concepts of Rehabilitation in Tuberculosis: A review of the literature, 1938-1947. By Norvin C. Kiefer, M.D., M.P.H. 8°, cloth, 398 pp. New York: National Tuberculosis Association, 1948. $3.50.

This book is a compilation of the literature on the subject of rehabilitation of the tuberculous. Fifteen of its sixteen chapters are abstracts of the current literature, and the last chapter is devoted to the comments of the author. This literature has sprung up chiefly in the past decade or fifteen years. It deals with the extent of this problem, the eligibility for rehabilitation services, suitable work for ex-patients, the contagious aspect of the disease and so forth. The administration as well as the cost of such a program also receives attention. The psychologic and the spiritual aspects of dealing with the chronically ill are also considered.

Although much has been written on rehabilitation and the author has abstracted more than a thousand articles, very little has actually been accomplished. This subject lends itself very well to lengthy discussions and seminars, but the actual concrete program of rehabilitation in the full sense of the word is beset with many difficulties. The protean nature of this disease and the contagiousness as well as the higher age of the present-day sanatorium population are major obstacles. However, the National Tuberculosis Association, through its state and city organizations, has dedicated itself to this task and made rehabilitation one of its goals. At least the community is made aware of its responsibilities to the handicapped person. Much education will be required on the part of labor unions and industries, as well as in legislative halls, regarding compensation laws, for the problem of employment of the handicapped to be solved.

This book is comprehensive in its scope and deals adequately with the new and very difficult subject of rehabilitation. The author knows his subject and speaks with authority on the various phases of a complicated and difficult process.

This book should prove useful to all tuberculosis workers.

The Story of Medicine. By Joseph Garland, M.D. 8°, cloth, 259 pp., with illustrations. Boston: Houghton Mifflin Company, 1949. $2.75.

In this short work the author has not undertaken a complete, systematic history of medicine, like those by Fielding Garrison and Cecilia Mettler. Rather, in a series of twenty-two editorial essays, he presents a popular synoptic review of the evolution of medical practice and science from the time of the prehistoric medicine man to the present day of specialists, of sulfonamides, of antibiotics, of blood fractioning and of radioactive isotopes. But he is concerned not merely with achievements but also with human personalities, and, without detailed biography, he recreates and revitalizes many "of the great physicians in the long line that has passed through the pages of medical history." Particularly is he to

be praised for the happy literary style of his work, and for his felicitous quotations from Homer, Martial, Shakespeare, "Everyman" and others. The book is well illustrated with twenty-three admirable original line drawings by Erwin Austin, and has a bibliography of thirty-two well selected titles. We are indeed fortunate to possess this fascinating volume by the editor of the *New England Journal of Medicine.*

Clinical Auscultation of the Heart. By Samuel A. Levine, M.D., and W. Proctor Harvey, M.D. 8°, cloth, 327 pp., with 86 illustrations. Philadelphia: W.B. Saunders Company, 1949. $6.50.

This book brings to the student and the general practitioner the results of a long and fruitful experience in cardiovascular auscultation. It is divided into four major sections: heart sounds, cardiac irregularities, cardiac murmurs and miscellaneous auscultatory findings. The last include fifteen conditions in which auscultation may be useful. The title is more restrictive than the subject matter, since the discussion is by no means limited to auscultation. Treatment, for example, is outlined for all the cardiac arrhythmias, and the x-ray findings in the congenital anomalies are described. Phonocardiograms are used very freely, but are correlated with electrocardiograms and with no other reference tracings such as phlebograms, which are essential in the analysis of diastolic phenomena. The illustrations are at times so reduced in size, and the sound tracings recorded at such slow speed, as to give little indication of the value of qualitative phonocardiography with modern technics. This, however, does not detract from the sound, clinical basis of the book. If the reader masters the stethoscopic technic, the auditory discrimination and the fundamental logic of these authors, most of the conditions described will not require graphic analysis. Outstanding are the discussions of gallop rhythms and systolic murmurs. The book can be recommended as a valuable guide to anyone aspiring to auscultatory perfection.

Lung Dust Lesions Versus Tuberculosis. By Lewis G. Cole, M.D. 4°, cloth, 474 pp., with 428 illustrations. White Plains, New York: American Medical Films, Incorporated, 1948. $10.00.

The author is a prolific writer and investigator of the old school, combining practical clinical knowledge with pure science. For years he has pioneered in the field of roentgenology. More recently, his chief interest has been the pathology of the lungs as related to pneumonoconiosis. He writes in a very delightful conversational style that makes for easy reading.

This is not a book on dust lesions or on tuberculosis as applied to its clinical aspects. The author deals chiefly with the intricacies of pathological interpretations of dust lesions in the lungs such as silicosis, tuberculosis and silicotuberculosis. According to him, many dusts other than silica cause lung dust lesions. In persons exposed to coal, talc, iron, copper, beryllium and so forth inhalation of such dusts, especially if they are also laden with micro-organisms, may cause fibrosis of the lungs. He also insists that chronic infections of the lungs and even tuberculosis cannot be distinguished pathologically from silicosis by the conventional light-field method of present-day microscopical examination. He believes that only by use of cross polaroid technic or cross nikols, especially lighted with a technic evolved by him, can silicosis be definitely distinguished from tuberculosis. He also deprecates the fact that patients with silcosis are kept from their occupations during the early stage of the disease, thus being unnecessarily deprived of their livelihood.

Many x-ray and pathological illustrations, excellently reproduced, accompany the text.

This book should be of particular interest to the research pathologist especially interested in the field of pneumonoconiosis.

Considerable more research and orientation in the field of industrial medicine will be needed before the author's view can be accepted. He apparently loves a good argument, and he has left himself wide open for many a controversy.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Rheumatic Fever: Nursing care in pictures. By Sabra S. Sadler, R.N., consultant nurse, rheumatic-fever program, Virginia State Health Department, and assistant professor of public-health nursing, Medical College of Virginia. 8°, cloth, 151 pp., with 204 illustrations. Philadelphia: J. B. Lippincott Company, 1949. $3.50.

This manual on the care of children suffering from rheumatic fever is written primarily for parents. The methods of present-day treatment are explained in detail, and the illustrations are self-explanatory. It is intended as a guide, with the understanding that all care and procedures should be based on specific orders from the physician in charge. An introduction on rheumatic fever from a medical point of view is written by Dr. Reno R. Porter, assistant professor of medicine and director of the Cardiac Foundation of the Medical College of Virginia, and consulting cardiologist, Virginia State rheumatic-fever program. The remaining chapters, written by Mrs. Sadler, who has been a special rheumatic-fever nurse with the Virginia Board of Health, since 1941, are devoted to the bed-rest treatment, personal care of the patient, care activities, diet, medications and treatment, and home teaching of school subjects. There is also a chapter on the social and emotional factors in the disease. The type and printing are excellent, but the ring type of binding is not suitable for a volume subject to hard usage. There is a good index. The manual should be in all public libraries and in the possession of parents with children suffering from rheumatic fever.

Clinical Aspects and Treatment of Surgical Infections. By Frank L. Meleney, M. D., associate professor of clinical surgery, College of Physicians and Surgeons, Columbia University and associate visiting surgeon, Presbyterian Hospital, New York City. With a foreword by Allen O. Whipple, M.D. 8°, cloth, 840 pp., with 287 illustrations. Philadelphia: W. B. Saunders Company, 1949. $12.00.

This special work covers the whole field of surgical infections from head to foot. It is intended as a companion volume to the author's *Treatise on Surgical Infections*, published in 1948. The material is well organized, and the text is well written. Numerous case histories are interspersed throughout the text. Selected lists of references are appended to the various chapters. There is a comprehensive author-subject index of fifty-eight pages. The book is well published and should be in all medical libraries and available to all surgeons.

Obstetric Analgesia and Anesthesia: Their effects upon labor and the child. By Franklin F. Snyder, M.D., associate professor of obstetrics and associate professor of anatomy, Harvard Medical School. 8°, cloth, 401 pp., with 114 illustrations and 18 tables. Philadelphia: W. B. Saunders Company, 1949. $6.50.

This new work is essential for all obstetricians and anesthetists. The material is well arranged and well written. The text is divided into two parts: respiratory injuries of the child; and the treatment of pain during labor. The first part discusses in detail the respiratory injuries before birth, including intrauterine pneumonia, atelectasis and asphyxia. The second considers all the anesthetics used during labor. Lists of references are appended to the various subjects, and there is a good index. The book should be in all medical libraries.

Your Child or Mine. The story of the cerebral-palsied child. By Mary L. H. Burton, executive secretary of the Westchester Cerebral Palsy Association. In collaboration with Sage H. Jennings. 12°, cloth, 64 pp., with illustrations. New York: Coward-McCann, Incorporated, 1949. $1.25.

This small volume relates the case histories of 6 children afflicted with cerebral palsy. It is written for the laity and shows what can be done for such children, especially socially,

if they receive the proper attention. The text is concluded with a list of cerebral-palsy associations and clinics. The book does not attempt to prescribe medically or surgically for the children. There is a short glossary of terms and a list of books and articles for further reading.

Diabetic Menus, Meals and Recipes. By Betty M. West. 8°, cloth, 254 pp. Garden City, New York: Doubleday and Company, Incorporated, 1949. $2.95.

This dietary manual was written primarily for diabetic patients and their families. Mrs. West acquired her knowledge at first hand, since she is a diabetic housewife. The soundness of her cookbook is attested by Dr. Rypins, a well known authority on diabetes. The book is well published, and there is a good index. It should prove valuable to those for whom it was written.

NOTICES

ANNOUNCEMENTS

Dr. Edmund F. Finnerty, Jr., announces the opening of his office for the practice of dermatology at 482 Commonwealth Avenue, Boston.

Dr. Aldo A. Luisada announces his appointment as assistant professor of medicine and program director of cardiology at University of Chicago School of Medicine, 710 South Wolcott Avenue, Chicago 12, Illinois, and the termination of his practice at 483 Beacon Street, Boston, on October 1, 1949.

Dr. William A. Lynch announces the opening of an office for the practice of obstetrics and gynecology at 1101 Beacon Street, Brookline, Massachusetts.

Dr. Albert O. Seeler announces the opening of an office for the practice of internal medicine at 1 Craigie Street, Cambridge.

SUFFOLK DISTRICT WOMAN'S AUXILIARY

The first meeting of the 1949-1950 season of the Suffolk District Woman's Auxiliary will be held on Thursday, October 6, at 2:30 p.m., in Sprague Hall, Boston Medical Library. The speakers will be Dr. A. J. A. Campbell, president of the Suffolk District Medical Society, and Miss Mary Jo Kraft, health education consultant for the United States Public Health Service, whose subject will be "How Doctors' Wives Can Help in the Tuberculosis Detection Campaign." Tea will be served after the meeting.

GREATER BOSTON MEDICAL TECHNOLOGISTS ASSOCIATION

A meeting of the Greater Boston Medical Technologists Association will be held in the lecture hall of the Boston Lying-in Hospital, 221 Longwood Avenue, Boston, on Tuesday, October 4, at 7:30 p.m. Dr. T. Hale Ham will speak on the subject "The Mechanism and Diagnosis of Hemolytic Anemias."

VETERANS ADMINISTRATION COURSE IN CLINICAL ELECTROCARDIOGRAPHY

A course in clinical electrocardiography will be given by Dr. David Littmann at the Veterans Administration Hospital, West Roxbury, Massachusetts, on Fridays from 4 to 5 p.m., beginning October 7.

Interested physicians and new students are invited.

NEW YORK ACADEMY OF MEDICINE

The Twenty-Second Graduate Fortnight of the New York Academy of Medicine will be held October 10 through 21, the subject being "Advances in Diagnostic Methods." The program includes morning panel discussions, afternoon hospital clinics, evening addresses and scientific exhibits and demonstrations.

Fellows of the Academy will be furnished registration c without application. For others, a registration card wil sent upon receipt of check for ten dollars, payable to Academy, and forwarded to New York Academy of Medici 2 East 103rd Street, New York 29, New York.

SOCIETY MEETINGS AND CONFERENCES

October 3–6. Association of Medical Illustrators. Page 472, issue September 22.

October 3–May 19. Massachusetts Department of Mental Hea Postgraduate Seminar in Neurology and Psychiatry. Page 286, issue August 18.

October 4. Boston City Hospital House Officers' Association. P 472, issue of September 22.

October 4. Greater Boston Medical Technologists Association. No above.

October 6. Suffolk District Woman's Auxiliary. Notice above.

October 7. Veterans Administration Course in Clinical Electr cardiography. Notice above.

October 10–21. New York Academy of Medicine. Notice above.

October 11–15. American Society of Clinical Pathologists. Dra Hotel, Chicago.

October 13. Mononucleosis. Dr. Andrew Contratto. Pentucke Association of Physicians. 8:30 p.m. Haverhill.

October 14. Tuberculosis Rehabilitation Society. Page 434, issue September 15.

October 19. Massachusetts Chapter of American Academy of Gener Practice. Page 434, issue of September 15.

October 24–26. National Gastroenterological Association. Page 25 issue of August 11.

October 24–28. American Public Health Association. Page 251, issu of August 11.

October 28. Massachusetts Psychiatric Society. Page 434, issue o September 15.

November 2. New England Obstetrical and Gynecological Society Hotel Somerset, Boston.

November 2–5. Pan-American Congress of Pediatrics. Page 251, issue of August 11.

November 3–5. American Association of Blood Banks. Page xi, issue of June 16.

November 7–9. National Society for Crippled Children and Adults Page 184, issue of July 28.

November 7–12. International College of Surgeons. Page 251, issue of August 11.

November 14–17. American Academy of Pediatrics. Page 251, issue of August 11.

November 16. Massachusetts State Society of Examining Physicians Page 324, issue of August 25.

December 28 and 29. American Association for the Advancement of Science. Page 350, issue of September 1.

February 20–23. American Academy of General Practice. Page 252 issue of August 11.

May 16–18. Massachusetts Medical Society. Annual Meeting. Hotel Statler, Boston.

July 17–22. International Congress for Scientific Research. Page xvi issue of September 1.

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, OCTOBER 6

THURSDAY, OCTOBER 6

2:30 p.m. Suffolk District Woman's Auxiliary. Sprague Hall, Boston Medical Library.

FRIDAY, OCTOBER 7

*9:00 a.m.–12:00 m. Combined Medical and Surgical Staff Rounds. Peter Bent Brigham Hospital.

*12:00 m. X-Ray Conference. Margaret Jewett Hall, Mount Auburn Hospital, Cambridge.

*1:30 p.m. Tumor Clinic. Out-Patient Department, Mount Auburn Hospital, Cambridge.

*4:00–5:00 p.m. Veterans Administration Course in Clinical Electrocardiography. Veterans Administration Hospital, West Roxbury.

MONDAY, OCTOBER 10

*11:30 a.m.–12:15 p.m. Chest X-Ray Conference. South End Health Unit, 57 East Concord Street, Boston. Dr. Cleaveland Floyd in charge.

*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.

TUESDAY, OCTOBER 11

*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.

*1:30–2:30 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

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*Open to the medical profession.